Have art, review further later if needed.

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=> fil medl drugu jic biosis embase wpix; d que 123; d que 125
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inventor search

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L19        10240 SEA MIYAZAKI M?/AU
L20         2856 SEA TAKAI S?/AU
L22          251 SEA (ARYL OR PHENYL)(3A)(DIESTER# OR DI ESTER#)
L23            3 SEA (L19 OR L20) AND L22


L19        10240 SEA MIYAZAKI M?/AU
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L24           58 SEA L19 AND L20 AND L21
L25           13 SEA ?PEPTIDE? AND L24

=> s l23 or l25
L26           15 L23 OR L25

=> fil capl; d que l1; d que l17; d que l18
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L11          577 SEA FILE=CAPLUS ABB=ON  TAKAI S?/AU
L15          372 SEA FILE=CAPLUS ABB=ON  (ARYL/OBI OR PHENYL/OBI)(L)DIESTER#/OBI

L17            2 SEA FILE=CAPLUS ABB=ON  (L10 OR L11) AND L15



L10         2690 SEA FILE=CAPLUS ABB=ON  MIYAZAKI M?/AU
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L12          132 SEA FILE=CAPLUS ABB=ON  L10 AND L11
L13       160422 SEA FILE=CAPLUS ABB=ON  ADHESION#/OBI
L14           15 SEA FILE=CAPLUS ABB=ON  L12 AND L13
L18           10 SEA FILE=CAPLUS ABB=ON  L14 AND PHARMAC?/SX,SC

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'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


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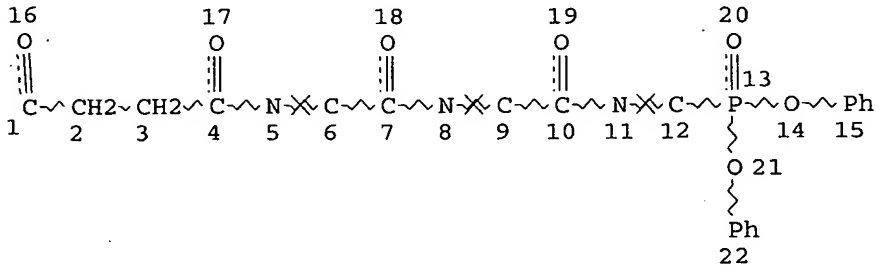


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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS  22

STEREO ATTRIBUTES: NONE
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=> s l1,l17,l18,l29
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=> dup rem l30,l26
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PROCESSING COMPLETED FOR L26
L31 24 DUP REM L30 L26 (8 DUPLICATES REMOVED)
ANSWERS '1-17' FROM FILE CAPLUS
ANSWERS '18-19' FROM FILE MEDLINE
ANSWERS '20-23' FROM FILE JICST-EPLUS
ANSWER '24' FROM FILE EMBASE

=> d ibib ed abs hitstr 1-17; d ibib ed abs 18-24

L31 ANSWER 1 OF 24 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2004:1019891 CAPLUS
DOCUMENT NUMBER: 141:420442
TITLE: Cardioprotective agent
INVENTOR(S): **Miyazaki, Mizuo; Takai, Shinji**
PATENT ASSIGNEE(S): Japan
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004100988	A1	20041125	WO 2004-JP6384	20040512
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1640020	A1	20060329	EP 2004-732417	20040512
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
PRIORITY APPLN. INFO.:			JP 2003-134487	A 20030513
			WO 2004-JP6384	W 20040512

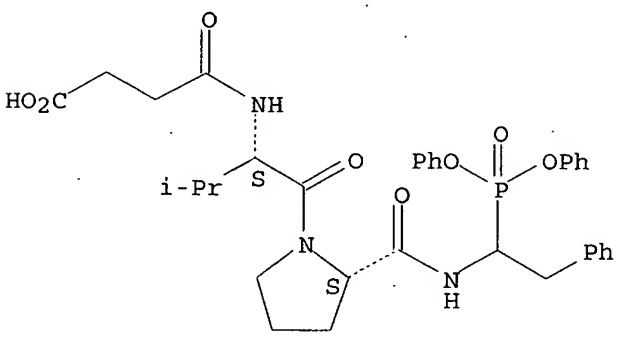
ED Entered STN: 26 Nov 2004
AB A medical agent capable of effective cardioprotection when the symptoms of hypertension, cardiomegaly, myocardial infarction, arteriosclerosis, diabetic or non-diabetic kidney diseases, arrhythmia accompanying re-stenosis, etc. after PTCA operation, cardiofibrosis and cardiac failure are concerned about. In particular, a medical agent comprising an effective amount of at least one protease inhibitor, i.v. or orally administered. The protease inhibitor is preferably a serine protease inhibitor which is specifically a chymotrypsin-like serine protease inhibitor. For example, use is made of a chymase inhibitor, viz. a

peptide derivative of aryl diester of α-aminoalkylphosphonic acid represented by Suc-Val-Pro-PheP(OPh)2, preferably its enantiomer Suc-Val-Pro-L-PheP(OPh)2.

IT **130727-22-9P 174391-82-3P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(peptide derivs. of **aryl diester** of α-aminoalkylphosphonic acids as protease inhibitors and cardioprotective agents)

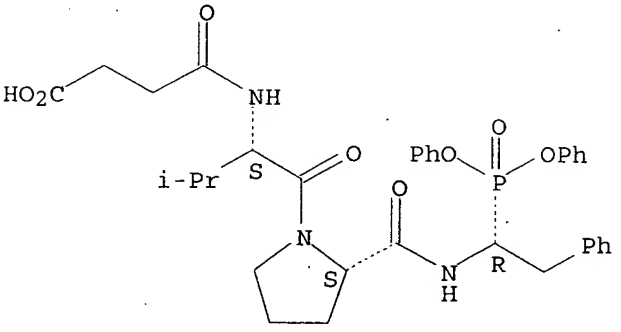
RN 130727-22-9 CAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 174391-82-3 CAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[(1R)-1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 2 OF 24 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2004:675660 CAPLUS
DOCUMENT NUMBER: 141:185127
TITLE: Drug for preventing, regulating or treating **adhesion**
INVENTOR(S): **Miyazaki, Mizuo; Takai, Shinji**
PATENT ASSIGNEE(S): Japan

SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004069276	A1	20040819	WO 2004-JP1111	20040204
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2006122101	A1	20060608	US 2005-544254	20050823 <--
PRIORITY APPLN. INFO.:			JP 2003-28743	A 20030205
			WO 2004-JP1111	W 20040204

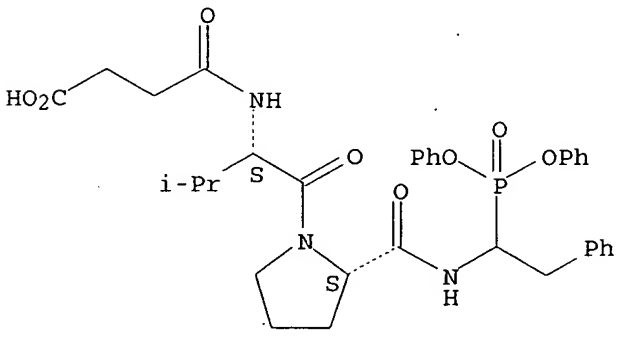
ED Entered STN: 19 Aug 2004

AB It is intended to provide a drug by which adhesion can be effectively prevented, regulated or treated in cases with the risk of visceral fusion caused by injury, inflammation, etc. before or after various surgical steps such as orthopedic or plastic surgeries relating to heart, breast, gynecol. cases, ophthalmic diseases and abdomen. Namely, a drug which contains at least one protease inhibitor in an ED and is to be used by i.v. administration, oral administration or transdermal application. It is preferable that the protease inhibitor is a serine protease inhibitor and the serine protease inhibitor is preferably a chymotrypsin-like serine protease inhibitor. As a specific example thereof, an α-aminoalkylsulfonic acid aryl diester peptide derivative Suc-Val-Pro-PheP(OPh)2, which is a chymase inhibitor, may be cited and an enantiomer Suc-Val-Pro-L-PheP(OPh)2, is preferred.

IT **130727-22-9 174391-80-1**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α-aminoalkylsulfonic acid **aryl diester** peptide derivs. as protease and chymase inhibitors for preventing and treating **adhesion** after surgery)

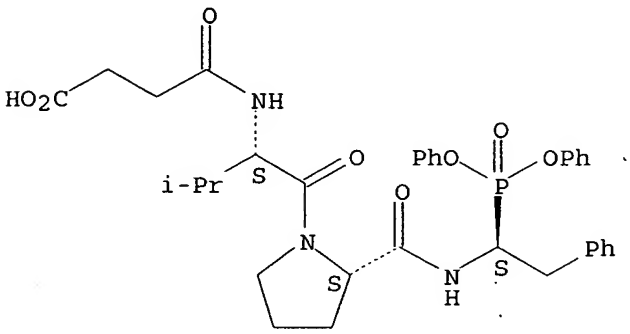
RN 130727-22-9 CAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 174391-80-1 CAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[(1S)-1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



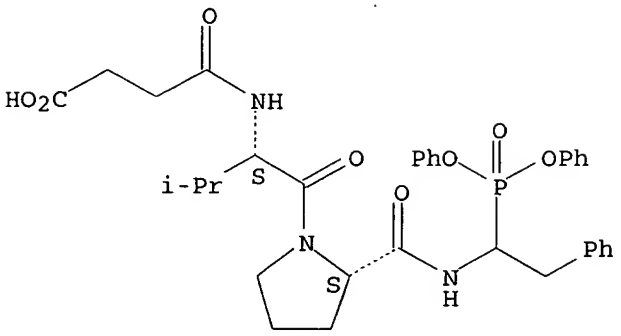
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 3 OF 24 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2004:80335 CAPLUS
DOCUMENT NUMBER: 140:122834
TITLE: Methods for preventing adhesion formation using peptidyl protease inhibitors
INVENTOR(S): **Miyazaki, Mizuo**
PATENT ASSIGNEE(S): Japan
SOURCE: U.S. Pat. Appl. Publ., 17 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004018984	A1	20040129	US 2003-602035		20030623
PRIORITY APPLN. INFO.:			US 2002-396493P	P	20020717

ED Entered STN: 01 Feb 2004
AB The present invention generally provides methods for the prevention or reduction of adhesion formation/reformation using protease inhibitors. More specifically, this invention provides methods for preventing or inhibiting postoperative adhesion formation/reformation in mammals following surgical or accidental injury or inflammation to the organs of the peritoneal or pleural cavity or other body spaces, using serine protease inhibitors, such as, for example, using chymase inhibitors (e.g., α-aminoalkylphosphonate derivs.) and the like.
IT **130727-22-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptidyl protease inhibitors and use in preventing adhesion formation after surgery)
RN 130727-22-9 CAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

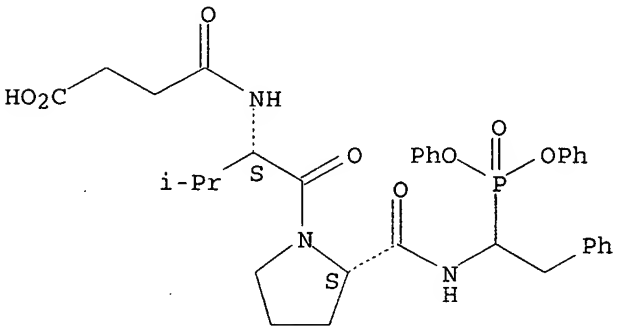


L31 ANSWER 4 OF 24 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2004:78778 CAPLUS
DOCUMENT NUMBER: 140:332085
TITLE: Significance of chymase inhibition for prevention of **adhesion** formation
AUTHOR(S): Okamoto, Yukiko; **Takai, Shinji**; **Miyazaki, Mizuo**
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Department of Pharmaceutical Sciences, Osaka, Takatsuki City, 589-8686, Japan
SOURCE: European Journal of Pharmacology (2004), 484(2-3), 357-359
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 30 Jan 2004
AB To clarify the role of chymase in adhesion formation, we investigated whether a chymase inhibitor could prevent adhesion formation after surgery in hamsters. Hamsters received a lesion produced by uterus scraping. A specific chymase inhibitor, 2-[4-(5-fluoro-3-methylbenzo[b]thiophen-2-yl)sulfonamido-3-(methanesulfonyl)phenyl]oxazole-4-carboxylic acid (TY-51184), or placebo was injected into the abdomen before closing and scores for adhesion formation were assessed at 1, 4, and 12 wk. A single peritoneal administration of TY-51184 significantly decreased the adhesion scores even at 12 wk (placebo, 2.80±0.20; chymase inhibitor, 1.60±0.31). Thus, chymase inhibitors may be a novel strategy to prevent adhesion formation.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 5 OF 24 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 2002:89522 CAPLUS
DOCUMENT NUMBER: 137:393
TITLE: Chymase inhibitor suppresses **adhesion** formation in a hamster experimental model
AUTHOR(S): Okamoto, Yukiko; **Takai, Shinji**; **Miyazaki, Mizuo**
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Takatsuki City, Osaka, 589-8686, Japan
SOURCE: European Journal of Pharmacology (2002), 435(2-3), 265-267

CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 01 Feb 2002
AB To clarify the role of chymase produced by mast cells in adhesion formation, we investigated the preventive effect of a specific chymase inhibitor, Suc-Val-Pro-Phep (OPh)2, on adhesion formation in a hamster exptl. model. Hamsters underwent resection of the right uterine body and then 10 μM Suc-Val-Pro-Phep (OPh)2 or placebo was injected into the abdomen. Two weeks after the operation, the scores for adhesion formation in the chymase inhibitor-treated group were significantly lower than that in the placebo-treated group (placebo-treated group, 3.60±0.22; chymase inhibitor-treated group, 2.10±0.22; P<0.01). This specific chymase inhibitor, Suc-Val-Pro-Phep (OPh)2, significantly suppressed the scores for adhesion formation in a hamster exptl. model. Thus, chymase may play an important role in the adhesion formation.
IT **130727-22-9**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chymase inhibitor suppresses **adhesion** formation in a hamster exptl. model)
RN 130727-22-9 CAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



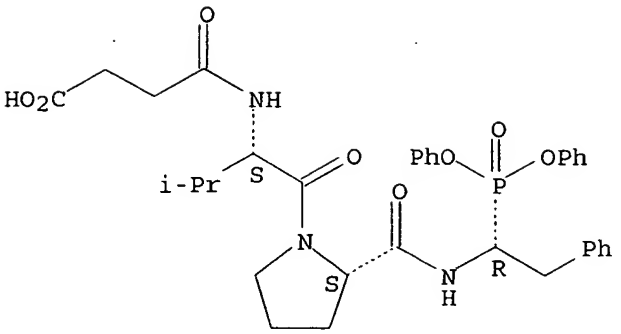
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 6 OF 24 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 2002:737105 CAPLUS
DOCUMENT NUMBER: 138:265581
TITLE: Oral administration of a novel chymase inhibitor, NK3201, prevents peritoneal **adhesion** formation in hamsters
AUTHOR(S): Okamoto, Yukiko; **Takai, Shinji**; **Miyazaki, Mizuo**
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Takatsuki City, 569-8686, Japan
SOURCE: Japanese Journal of Pharmacology (2002), 90(1), 94-96
CODEN: JJPAAZ; ISSN: 0021-5198
PUBLISHER: Japanese Pharmacological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

ED Entered STN: 29 Sep 2002
AB We investigated the preventive effect of an orally active chymase inhibitor, NK3201 (2-(5-formylamino-6-oxo-2-phenyl-1,6-dihydropyrimidine-1-yl)-N-[{3,4-dioxo-1-phenyl-7-(2-pyridyloxy)}-2-heptyl]acetamide), on the adhesion formation in a hamster exptl. model. Hamsters were administered orally once daily with 30 mg/kg of NK3201 or placebo from 3 days before uterus scraping to 7 days after it. A significant increase of chymase activity in the injured uterus was reduced by treatment with NK3201. The score of adhesion formations in the chymase inhibitor-treated group was significantly decreased in comparison with that in the placebo-treated group ($P<0.01$). Oral administration of NK3201 may be a useful drug for prevention of peritoneal adhesion formation.
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 7 OF 24 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1209247 CAPLUS
DOCUMENT NUMBER: 144:32161
TITLE: Effect of chymase on intraocular pressure in rabbits
AUTHOR(S): Konno, Takashi; Maruichi, Midori; **Takai, Shinji**; Oku, Hidehiro; Sugiyama, Tetsuya; Uchibori, Takehiro; Nagai, Akihiko; Kogi, Kentaro; Ikeda, Tsunehiko; **Miyazaki, Mizuo**
CORPORATE SOURCE: Drug Research Section II, Fukushima Research Laboratories, TOA EIYO LTD., Fukushima City, Fukushima, 960-0280, Japan
SOURCE: European Journal of Pharmacology (2005), 524(1-3), 132-137
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 15 Nov 2005
AB Chymase is a chymotrypsin-like serine protease that is stored exclusively in the secretory granules of mast cells and converts big endothelins to endothelin-1 (1-31). The aim of this study was to evaluate the effect of chymase on intraocular pressure in rabbits. Chymase injection (3 and 10 mU) resulted in a trend toward increased intraocular pressure and a significant increase in intraocular pressure at a dose of 10 mU compared with the control. A specific chymase inhibitor, Suc-Val-Pro-PheP(OPh)2, attenuated the ocular hypertension induced by chymase. Endothelin-1 (1-31) also caused ocular hypertension, which was inhibited by a selective endothelin ETA receptor antagonist, cyclo(D-Asp-Pro-D-Val-Leu-D-Trp) (BQ-123). Moreover, chymase-induced ocular hypertension was inhibited by BQ-123. These results suggest that chymase influences the regulation of intraocular pressure, and it is likely that the formation of endothelin-1 (1-31) and subsequent activation of endothelin ETA receptors are involved in the development of ocular hypertension induced by chymase.
IT **174391-82-3**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of chymase on intraocular pressure in rabbits)
RN 174391-82-3 CAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[(1R)-1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 8 OF 24 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:156881 CAPLUS
DOCUMENT NUMBER: 142:367175
TITLE: Inhibition of transforming growth factor-β activation is a novel effect of chymase inactivation
AUTHOR(S): **Takai, S.; Miyazaki, M.**
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Takatsuki City, 569-8686, Japan
SOURCE: Letters in Drug Design & Discovery (2005), 2(1), 19-22
CODEN: LDDDAW; ISSN: 1570-1808
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 24 Feb 2005
AB Chymase activates latent transforming-growth factor-β to transforming-growth factor-β in vitro. Recent papers demonstrate that transforming-growth factor-β levels and tissue fibrosis were significantly reduced by chymase inhibitors in the exptl. models. Thus, transforming-growth factor-β-related diseases such as fibrosis may become a novel target of chymase inhibitors.
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 9 OF 24 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:351637 CAPLUS
DOCUMENT NUMBER: 140:350627
TITLE: Chymase inhibitor-containing pharmaceuticals for surgery for glaucoma
INVENTOR(S): **Miyazaki, Mizuo; Takai, Shinji**
PATENT ASSIGNEE(S): Toa Eiyo, Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2004131442	A2	20040430	JP 2002-298825	20021011
PRIORITY APPLN. INFO.:			JP 2002-298825	20021011

ED Entered STN: 30 Apr 2004

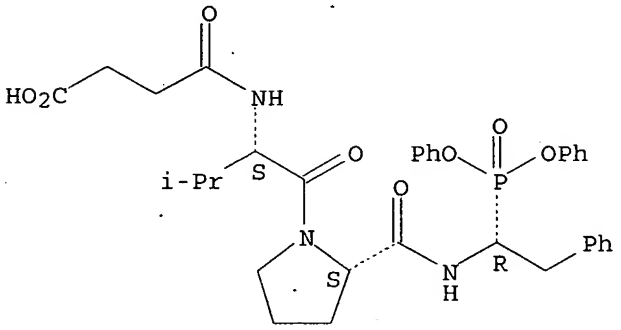
AB Title pharmaceuticals contain (optically active) di-Ph 1-(N-succinyl-L-valyl-L-prolylamino)-2-phenylethanephosphonate (VPF) as active ingredient. Thus, application of VPF on sclera flap in trabeculectomy in dogs resulted in bleb formation rich in blood vessels with no tissue adhesion.

IT **174391-82-3P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of valylproline derivative as chymase inhibitor for surgery for glaucoma)

RN 174391-82-3 CAPLUS

CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[(1R)-1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

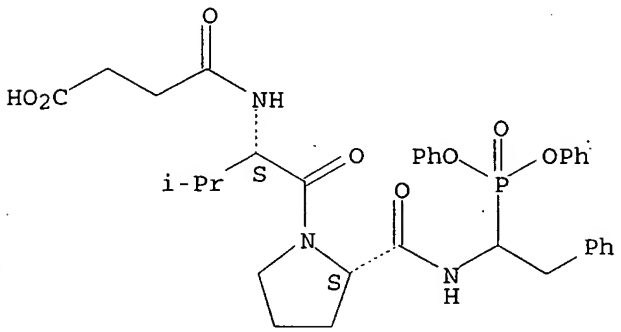


IT **130727-22-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of valylproline derivative as chymase inhibitor for surgery for glaucoma)

RN 130727-22-9 CAPLUS

CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

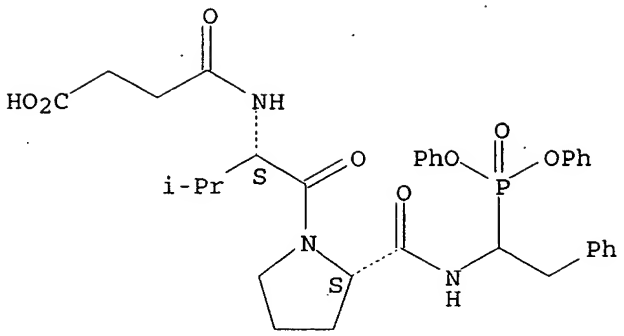
Absolute stereochemistry.



L31 ANSWER 10 OF 24 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:184001 CAPLUS

DOCUMENT NUMBER: 141:218544
TITLE: Attenuation of **adhesion** formation after cardiac surgery with a chymase inhibitor in a hamster model
AUTHOR(S): Soga, Yoshiharu; **Takai, Shinji**; Koyama, Tadaaki; Okamoto, Yukiko; Ikeda, Tadashi; Nishimura, Kazunobu; **Miyazaki, Mizuo**; Komeda, Masashi
CORPORATE SOURCE: Department of Cardiovascular Surgery, Kyoto University Graduate School of Medicine, Kyoto, 606-8507, Japan
SOURCE: Journal of Thoracic and Cardiovascular Surgery (2004), 127(1), 72-78
CODEN: JTCSAQ; ISSN: 0022-5223
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 08 Mar 2004
AB Objective: Chymase is one of the inflammatory mediators and is released from mast cells, which are closely associated with adhesion formation. Chymase also activates transforming growth factor β1, which promotes tissue fibrosis. However, the role of chymase in cardiac adhesion formation has not yet been elucidated. We have assessed whether a specific chymase inhibitor, Suc-Val-Pro-PheP (OPh)2, prevents postoperative cardiac adhesions in hamsters. Methods: In 66 hamsters the epicardium was abraded, and then either chymase inhibitor or placebo was injected into the left thoracic cavity, leaving the pericardium open. Cardiac chymase activity, the level of transforming growth factor β1 in the pleural fluid, and the d. of epicardial mast cells were measured 3 days postoperatively. The degree of adhesion formation was evaluated macroscopically and histol. 2 wk postoperatively by using a grading score ranging from 0 (no adhesions) to 4 (severe adhesions). Results: The cardiac chymase activity and level of transforming growth factor β1 were lower in the chymase inhibitor-treated group compared with in the placebo-treated group (45.8 ± 18.7 vs 79.7 ± 13.7 μU/mg protein [$P < .025$] and 15.6 ± 6.5 vs 33.2 ± 9.8 μg/mL [$P < .01$], resp.). The d. of mast cells was higher in the placebo-treated group, and there was suppression to 60% of this value in the chymase inhibitor-treated group. The adhesion scores were lower in the chymase inhibitor-treated group compared with in the placebo-treated group (1.3 ± 1.3 vs 3.0 ± 1.1, $P < .01$). Conclusion: Use of a chymase inhibitor suppresses not only cardiac chymase activity but also the level of transforming growth factor β1, and this results in a reduction in postoperative cardiac adhesion.
IT **130727-22-9**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(administration of specific chymase inhibitor Suc-Val-Pro-Phep (OPh)2 attenuates cardiac chymase activity, level of transforming growth factor β1 and postoperative cardiac **adhesions** in hamster model)
RN 130727-22-9 CAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 11 OF 24 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:918694 CAPLUS
DOCUMENT NUMBER: 140:777
TITLE: Benzothiophen sulfonamide analogs as bioadhesion inhibitors
INVENTOR(S): **Miyazaki, Mitsuo; Takai, Shinji;** Sato, Shoji
PATENT ASSIGNEE(S): Toa Eiyo, Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 29 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
JP 2003335670	A2	20031125	JP 2003-70126		20030314
PRIORITY APPLN. INFO.:			JP 2002-72306	A	20020315

OTHER SOURCE(S): MARPAT 140:777
ED Entered STN: 25 Nov 2003
AB Benzothiophen sulfonamide analogs (I; Markush's structures given) and their pharmaceutically acceptable salts are claimed as bioadhesion inhibitors. I were prepared, and their chymase- and bioadhesion-inhibiting activities were tested. Formulation examples of tablets, injections, suppositories, and eyedrops were given.

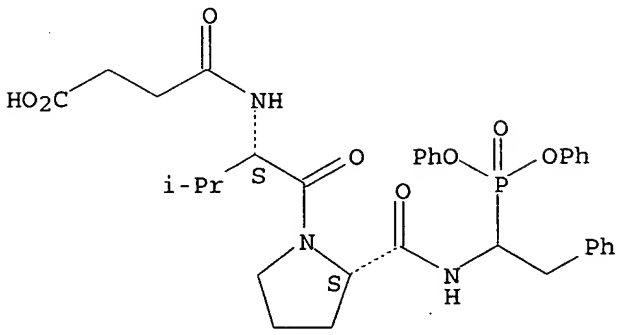
L31 ANSWER 12 OF 24 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:91709 CAPLUS
DOCUMENT NUMBER: 139:95180
TITLE: Mechanisms of angiotensin II type 1 receptor blocker for anti-atherosclerotic effect in monkeys fed a high-cholesterol diet
AUTHOR(S): **Takai, Shinji**; Kim, Shokei; Sakonjo, Hiroshi; **Miyazaki, Mizuo**
CORPORATE SOURCE: Osaka Medical College, Department of Pharmacology, Osaka City University Medical School, Osaka, Takatsuki City, Abeno-ku, Japan
SOURCE: Journal of Hypertension (2003), 21(2), 361-369
CODEN: JOHYD3; ISSN: 0263-6352
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal

LANGUAGE: English
ED Entered STN: 06 Feb 2003
AB To clarify the mechanism of the anti-atherosclerotic effect of angiotensin II type 1 receptor blocker (ARB) in primates, we investigated whether an ARB (CS-866) affects the serum markers of inflammation and growth factors, and the endothelial function in monkeys fed a high-cholesterol diet. Monkeys fed a high-cholesterol diet for 6 mo were divided into two groups: one group was given an ARB, CS-866 (10 mg/kg per.day), and the other group was not. The control group was fed a normal diet. Blood pressure and the plasma cholesterol level were not affected by CS-866. Plasma levels of angiotensin II, renin, angiotensin converting enzyme and chymase were not changed by the high-cholesterol diet, whereas vascular angiotensin converting enzyme, but not chymase, was significantly increased. Serum levels of macrophage-colony stimulating factor, transforming growth factor-β1 and intracellular adhesion mol.-1 were significantly increased in monkeys fed a high-cholesterol diet but they were suppressed by CS-866. The relaxation response of isolated carotid arteries to acetylcholine was suppressed in the high-cholesterol group, whereas it was improved by CS-866. CS-866 reduced lipid deposition along with the suppression of serum macrophage-colony stimulating factor, transforming growth factor-β1 and intracellular adhesion mol.-1, and the improvement of vascular functions, suggesting that ARB has multiple mechanisms for reducing lipid deposition in primates.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 13 OF 24 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:761196 CAPLUS
DOCUMENT NUMBER: 138:314202
TITLE: Lengthy suppression of vascular proliferation by a chymase inhibitor in dog grafted veins
AUTHOR(S): Tsunemi, Koutaro; **Takai, Shinji**; Nishimoto, Masayoshi; Yuda, Atsushi; Jin, Denan; Sakaguchi, Masato; Sawada, Yoshihide; Asada, Kunio; Kondo, Keiichiro; Sasaki, Shinjira; **Miyazaki, Mizuo**
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Osaka, 569-8686, Japan
SOURCE: Journal of Thoracic and Cardiovascular Surgery (2002), 124(3), 621-625
CODEN: JTCSAQ; ISSN: 0022-5223
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 08 Oct 2002
AB In this study the authors investigated the longterm effect of the chymase inhibitor Suc-Val-Pro-Phep(OPh)2 on intimal hyperplasia in dog grafted veins after bypass surgery. Twelve beagle dogs were studied. ACE and chymase activities, as well as total angiotensin II-forming activity were reported; and intimal area, medial area and ratio of intimal area to medial area were given. The results demonstrated that direct and single infiltration of grafting veins to a chymase inhibitor maintained suppression of chymase activity and vascular proliferation 3 mo after bypass surgery.
IT **130727-22-9**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lengthy suppression of vascular proliferation by chymase inhibitor in dog grafted veins in relation to prevention of intimal hyperplasia)
RN 130727-22-9 CAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-

(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

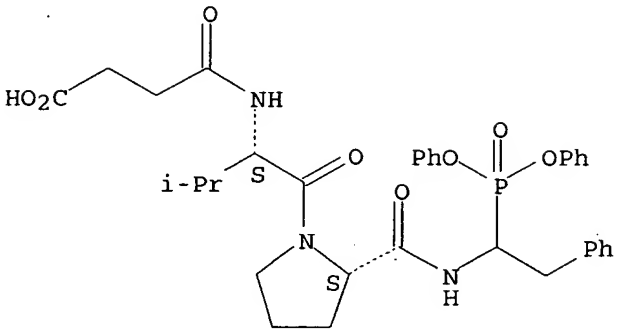
Absolute stereochemistry.



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 14 OF 24 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:371857 CAPLUS
DOCUMENT NUMBER: 137:166726
TITLE: Effects of chymase on human dermal microvascular endothelial cells and human dermal fibroblasts
AUTHOR(S): Tanabe, Yuko; Soma, Yoshinao; **Takai, Shinji**; **Miyazaki, Mizuo**; Mizoguchi, Masako
CORPORATE SOURCE: Dep. Dermatol., St. Marianna Univ. Sch. Med., Kawasaki, 216-8511, Japan
SOURCE: Nippon Hifuka Gakkai Zasshi (2002), 112(3), 239-246
CODEN: NHKZAD; ISSN: 0021-499X.
PUBLISHER: Nippon Hifuka Gakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
ED Entered STN: 20 May 2002
AB Chymase is a proteolytic enzyme present in mast cell granules that is released by mast cell degranulation with tryptase, histamines, and other mediators. To elucidate the roles of mast cells in various biol. processes, including fibrosis and wound repair, it is necessary to know the effects of chymase on fibroblasts and vascular endothelial cells. We examined the effect of human chymase on human dermal microvascular endothelial cells (HDMEC) and human dermal fibroblasts (HDF). Chymase did not affect HDMEC growth, but it did stimulate the proliferation of HDF at 1 nM concentration This growth-promoting activity was completely inhibited by the addition of the chymase substrate peptide, Suc-Val-Pro-PheP(OPh)2. Chymase did not have any effect on ICAM-1 or VCAM-1 expression in HDMEC and HDF. The present study suggests that the mitogenic effect of chymase released from mast cells on dermal fibroblasts may be involved in some pathol. and physiol. processes. Another chymase inhibitory agent, which is a quinazoline derivative, stimulated the growth of HDMEC and enhanced VCAM-1 expression in the cells, suggesting an angiogenic effect.
IT **130727-22-9**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(effects of chymase on human dermal microvascular endothelial cells and human dermal fibroblasts)
RN 130727-22-9 CAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L31 ANSWER 15 OF 24 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:836109 CAPLUS
DOCUMENT NUMBER: 139:63252
TITLE: Chymase Inhibitor, BCEAB, Suppressed Peritoneal **Adhesion** Formation in Hamster
AUTHOR(S): Okamoto, Yukiko; **Takai, Shinji**; **Miyazaki, Mizuo**
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Takatsuki City, 569-8686, Japan
SOURCE: Journal of Surgical Research (2002), 107(2), 219-222
CODEN: JSGRA2; ISSN: 0022-4804
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 04 Nov 2002
AB Background. Mast cells are closely related to adhesion formation, while it has been unclear which factor in mast cells plays an important role in the development of adhesion formation. To clarify the role of chymase produced from mast cells in adhesion formation, we investigated the preventive effect of a specific chymase inhibitor, BCEAB, on adhesion formation in a hamster exptl. model. Materials and methods. Hamsters were administered orally once daily with 100 mg/kg of BCEAB or placebo from the operated day to 1 wk after the operation. The uterus was grasped and denuded by a swab. Results. One week after the operation, the scores for adhesion formation in the chymase inhibitor-treated group were significantly decreased in comparison with those in the placebo-treated group (placebo-treated group, 2.80; chymase inhibitor-treated group 1.60). The chymase activity in the injured uterus was also significantly suppressed in the chymase inhibitor-treated group (placebo-treated group, 17.3 mU/mg protein; chymase inhibitor-treated group 9.60). After scraping the uterus, the level of transforming growth factor-β in the peritoneal fluid was significantly increased in the placebo-treated group, while it was suppressed to 70% by the treatment with BCEAB. Conclusions. The specific chymase inhibitor BCEAB may be a useful drug for prevention of adhesion formation.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

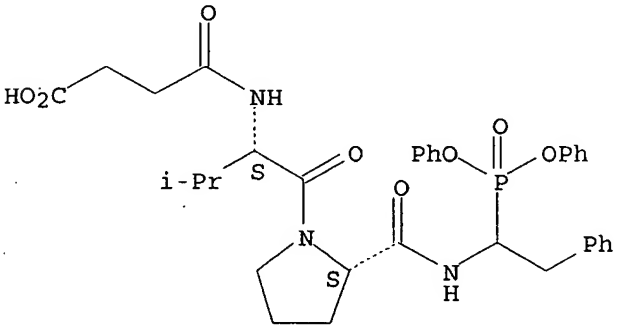
L31 ANSWER 16 OF 24 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:411492 CAPLUS
DOCUMENT NUMBER: 138:19331
TITLE: Antiatherosclerotic efficacy of olmesartan
AUTHOR(S): **Miyazaki, M.**; **Takai, S.**

CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Osaka, 569-8686, Japan
SOURCE: Journal of Human Hypertension (2002), 16(Suppl. 2), S7-S12
CODEN: JHHYEN; ISSN: 0950-9240
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 02 Jun 2002
AB The possible inhibition of lipid deposition into vascular tissues by a novel angiotensin II type 1 receptor antagonist, olmesartan, was investigated in a primate high-cholesterol model. Twelve monkeys that were fed a high-cholesterol (4% cholesterol and 6% corn oil) diet for 6 mo were divided into two groups: one group was given olmesartan medoxomil (10 mg/kg per day), and the other group was given no medication. A further control group of six monkeys was fed a normal diet throughout the study. The level of low-d. lipoprotein (LDL) cholesterol was increased by the high-cholesterol diet, whereas that of high-d. lipoprotein (HDL) cholesterol was decreased. Olmesartan decreased the areas of lipid deposition on the aortic surface and intimal cross-section area, but not the mean blood pressure and the levels of LDL and HDL cholesterol. The relaxation response of isolated carotid arteries to acetylcholine was suppressed in the high-cholesterol group, but this was improved by olmesartan. Olmesartan inhibited the accumulation of macrophages in the intimal layer. Serum levels of transforming growth factor (TGF)-β1, macrophage colony-stimulating factor (M-CSF) and intracellular adhesion mol. (ICAM)-1 were increased in monkeys fed the high-cholesterol diet, but they were suppressed by olmesartan, although the decrease was not significant. Olmesartan reduced lipid deposition, accompanied by the improvement of vascular functions and the inhibition of macrophage accumulation in the intimal layer and showed a trend towards the suppression of serum TGF-β1, M-CSF and ICAM-1.
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 17 OF 24 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:95832 CAPLUS
DOCUMENT NUMBER: 132:274101
TITLE: Inhibition of chymase reduces vascular proliferation in dog grafted veins
AUTHOR(S): **Takai, S.**; Yuda, A.; Jin, D.; Nishimoto, M.; Sakagichi, M.; Sasaki, S.; **Miyazaki, M.**
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Takatsuki City, Osaka, Japan
SOURCE: FEBS Letters (2000), 467(2,3), 141-144
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 10 Feb 2000
AB We investigated the effect of a chymase inhibitor Suc-Val-Pro-PheP(OPh)2 on the proliferation of the grafted vein in dog. By 28 days after the operation, the mean intimal area of the grafted vein in the placebo group was 3.24±0.32 mm2. The intimal area of the grafted vein in the chymase inhibitor-treated group was reduced to 63.9%. In the placebo group, the activities of chymase and angiotensin-converting enzyme in grafted vein were significantly increased 15- and 2-fold, resp. In the chymase inhibitor-treated group, chymase activity in the grafted veins was decreased significantly. These findings suggest that inhibition of chymase appears useful for preventing vascular proliferation.

IT **130727-22-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of chymase reduces vascular proliferation in dog grafted veins)
RN 130727-22-9 CAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 18 OF 24 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2004481058 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15449158
TITLE: Effect of chymase-dependent transforming growth factor beta on peritoneal **adhesion** formation in a rat model.
AUTHOR: Okamoto Yukiko; **Takai Shinji**; **Miyazaki Mizuo**
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Takatsuki, Osaka 589-8686, Japan.
SOURCE: Surgery today, (2004) Vol. 34, No. 10, pp. 865-7. Journal code: 9204360. ISSN: 0941-1291.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200502
ENTRY DATE: Entered STN: 28 Sep 2004
Last Updated on STN: 10 Feb 2005
Entered Medline: 9 Feb 2005
ED Entered STN: 28 Sep 2004
Last Updated on STN: 10 Feb 2005
Entered Medline: 9 Feb 2005
AB PURPOSE: To clarify the role of chymase produced from mast cells, which are closely related to **adhesion** formation, we investigated the preventive effect of a chymase inhibitor on **adhesion** formation in a rat model. METHODS: A lesion was created in rats by uterus scraping, and a chymase inhibitor, Suc-Val-Pro-Phep(OPh)2 (10 microM), or a placebo was injected into the abdomen. The level of transforming growth factor

beta (TGF-beta) in the peritoneal fluid was also measured. RESULTS: By 2 weeks after the operation, the scores for **adhesion** formation in the chymase inhibitor-treated group were significantly lower than those in the placebo-treated group, at 1.64 +/- 0.34 and 3.27 +/- 0.19, respectively ($P < 0.01$). After scraping the uterus, the level of TGF-beta in the peritoneal fluid was significantly higher in the placebo-treated group, whereas it was significantly suppressed by the chymase inhibitor. CONCLUSIONS: Chymase may play an important role in **adhesion** formation aided by TGF-beta.

L31 ANSWER 19 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2003520317 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12009365
TITLE: Chymase inhibitors may prevent postoperative **adhesion** formation.
AUTHOR: Okamoto Yukiko; **Takai Shinji**; Yamada Mayumi; **Miyazaki Mizuo**
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Takatsuki City, Osaka, Japan.
SOURCE: Fertility and sterility, (2002 May) Vol. 77, No. 5, pp. 1044-8.
Journal code: 0372772. ISSN: 0015-0282.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200311
ENTRY DATE: Entered STN: 6 Nov 2003
Last Updated on STN: 19 Dec 2003
Entered Medline: 26 Nov 2003
ED Entered STN: 6 Nov 2003
Last Updated on STN: 19 Dec 2003
Entered Medline: 26 Nov 2003
AB OBJECTIVE: To clarify the role of chymase produced from mast cells in **adhesion** formation, we measured chymase activity level and investigated the preventive effect of a chymase inhibitor, Suc-Val-Pro-Phe(p)(OPh)(2), on the postoperative **adhesion** formation. DESIGN: Prospective randomized study using a surgical model for **adhesion** formation. SETTING: Clean hamsters in an academic research environment. ANIMAL(S): Sixty-seven female Syrian hamsters. INTERVENTION(S): Hamsters were given a lesion, produced by uterus scraping, and the chymase inhibitor (10 microM) or placebo was injected into the abdomen. Chymase activities in uteri were measured 3 days after the operation, and the scores of **adhesion** formations were assessed at 2 weeks. MAIN OUTCOME MEASURE(S): Measurement of chymase activity and scoring of **adhesion** formation were performed. RESULT(S): A significant increase of chymase activity in the injured uterus reduced by treatment with the chymase inhibitor. The scores of **adhesion** formations in the chymase inhibitor-treated group were significantly decreased in comparison with those in the placebo-treated group. CONCLUSION(S): Chymase contained in mast cells plays an important role in **adhesion** formation, and a chymase inhibitor may be a useful drug for prevention of **adhesion** formation.

L31 ANSWER 20 OF 24 JICST-EPlus COPYRIGHT 2006 JST on STN
ACCESSION NUMBER: 1040259624 JICST-EPlus
TITLE: Significance of chymase-dependent transforming growth factor-B formation on **adhesion** formation
AUTHOR: **TAKAI S**; OKAMOTO Y; **MIYAZAKI M**
CORPORATE SOURCE: Osaka Medical Coll., Takatsuki, Jpn

SOURCE: J Pharmacol Sci, (2004) vol. 94, no. Supplement 1, pp. 201P. Journal Code: G0813A
ISSN: 1347-8613
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Preprint
LANGUAGE: English
STATUS: New

L31 ANSWER 21 OF 24 JICST-EPlus COPYRIGHT 2006 JST on STN
ACCESSION NUMBER: 1030277071 JICST-EPlus
TITLE: A novel therapeutics for prevention of **adhesion** formation with chymase inhibitors in the hamster **adhesion** model.
AUTHOR: OKAMOTO Y; **TAKAI S**; **MIYAZAKI M**
CORPORATE SOURCE: Osaka Med. Coll., Osaka, Jpn
SOURCE: J Pharmacol Sci, (2003) vol. 91, no. Supplement 1, pp. 165P. Journal Code: G0813A
ISSN: 1347-8613
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Preprint
LANGUAGE: English
STATUS: New

L31 ANSWER 22 OF 24 JICST-EPlus COPYRIGHT 2006 JST on STN
ACCESSION NUMBER: 1020369441 JICST-EPlus
TITLE: Interaction of Human Vascular Smooth Muscle Cells with Extracellular Matrix: Effect of Mast Cell Chymase.
AUTHOR: OKUMURA K; KATAYAMA S; SAKAGUCHI M; **TAKAI S**; **MIYAZAKI M**
CORPORATE SOURCE: Osaka Medical Coll., Osaka, Jpn
SOURCE: Jpn J Pharmacol, (2002) vol. 88, no. Supplement 1, pp. 184. Journal Code: G0813A
CODEN: JJPAAZ; ISSN: 0021-5198
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Preprint
LANGUAGE: English
STATUS: New

L31 ANSWER 23 OF 24 JICST-EPlus COPYRIGHT 2006 JST on STN
ACCESSION NUMBER: 1020369172 JICST-EPlus
TITLE: Chymase inhibitor prevents the **adhesion** formation after surgical operation.
AUTHOR: OKAMOTO Y; **TAKAI S**; **MIYAZAKI M**
CORPORATE SOURCE: Osaka Medical Coll., Osaka, Jpn
SOURCE: Jpn J Pharmacol, (2002) vol. 88, no. Supplement 1, pp. 116. Journal Code: G0813A
CODEN: JJPAAZ; ISSN: 0021-5198
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Preprint
LANGUAGE: English
STATUS: New

L31 ANSWER 24 OF 24. EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2004356990 EMBASE
TITLE: Human chymase degrades human fibronectin [1].
AUTHOR: Okumura K.; **Takai S.**; Muramatsu M.; Katayama S.; Sakaguchi M.; Kishi K.; Jin D.; **Miyazaki M.**
CORPORATE SOURCE: S. Takai, Department of Pharmacology, Osaka Medical College, 2-7 Daigaku-machi, Osaka 569-8686, Takatsuki,

Japan. pha010@art.osaka-med.ac.jp
SOURCE: Clinica Chimica Acta, (2004) Vol. 347, No. 1-2, pp. 223-225.
Refs: 7
ISSN: 0009-8981 CODEN: CCATAR
PUBLISHER IDENT.: S 0009-8981(04)00221-9
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Letter
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Sep 2004
Last Updated on STN: 2 Sep 2004
ED Entered STN: 2 Sep 2004
Last Updated on STN: 2 Sep 2004
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

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FILE 'REGISTRY' ENTERED AT 11:36:41 ON 27 SEP 2006
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DICTIONARY FILE UPDATES:  26 SEP 2006  HIGHEST RN 908803-03-2

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experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html
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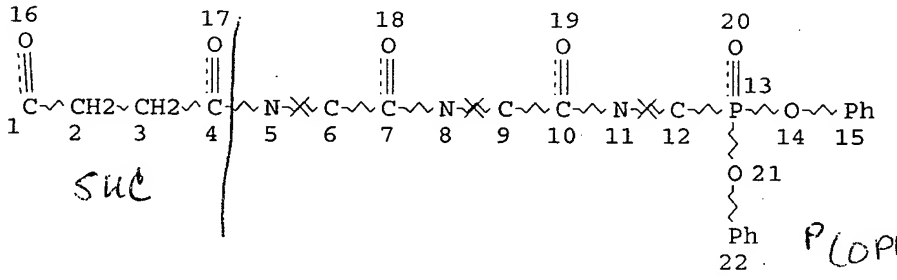
L6 STR



SUC

= ring or chain bonds & nodes (i.e. any amino acid)

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NSPEC   IS RC     AT   6
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  22

STEREO ATTRIBUTES: NONE
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100.0% PROCESSED     199 ITERATIONS                    8 ANSWERS
SEARCH TIME: 00.00.01
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this structure will retrieve "flat" structures & "D" & "L" forms

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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 27 Sep 2006 VOL 145 ISS 14
FILE LAST UPDATED: 26 Sep 2006 (20060926/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html
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L37 19 L8

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L38 9 L37 NOT L30

printed w/ inventor search

=> fil prousddr synthline; s l8
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FILE 'SYNTHLINE' ENTERED AT 11:52:29 ON 27 SEP 2006
COPYRIGHT (C) 2006 Prous Science

L39 2 L8

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FILE 'WPIX' ENTERED AT 11:52:39 ON 27 SEP 2006
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FILE LAST UPDATED: 22 SEP 2006 <20060922/UP>
MOST RECENT DERWENT UPDATE: 200661 <200661/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://scientific.thomson.com/support/patents/coverage/latestupdates/

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>>> PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
http://www.stn-international.de/stndatabases/details/ipc_reform.html and
http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf <<<

>>> FOR FURTHER DETAILS ON THE FORTHCOMING DERWENT WORLD PATENTS
    INDEX ENHANCEMENTS PLEASE VISIT:
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<
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L6               STR
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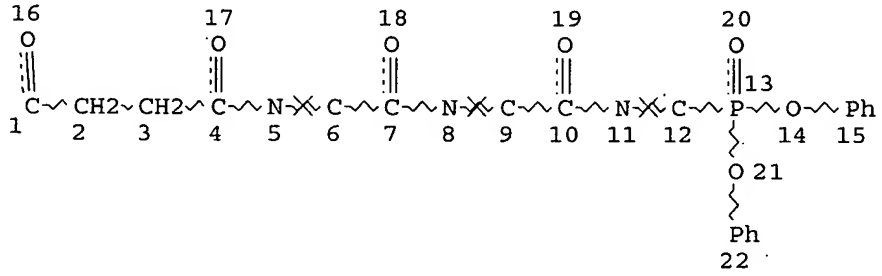


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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  22

STEREO ATTRIBUTES: NONE
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100.0% PROCESSED       2 ITERATIONS                          1 ANSWERS
SEARCH TIME: 00.00.01


=> d que nos l36
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L34            1 SEA FILE=WPIX ABB=ON  L33/DCR
L35            1 SEA FILE=WPIX ABB=ON  RADD0D/DCN OR 399806-1-0-0/DCRE
L36            1 SEA FILE=WPIX ABB=ON  L34 OR L35


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ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
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PROCESSING COMPLETED FOR L38
PROCESSING COMPLETED FOR L36
PROCESSING COMPLETED FOR L39
L40           12 DUP REM L38 L36 L39 (0 DUPLICATES REMOVED)
                 ANSWERS '1-9' FROM FILE CAPLUS
                 ANSWER '10' FROM FILE WPIX
                 ANSWER '11' FROM FILE PROUSDDR
                 ANSWER '12' FROM FILE SYNTHLINE

=> d ibib ed abs hitstr 1-10; d iall 11-12; fil hom

L40  ANSWER 1 OF 12  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2002:929299  CAPLUS
DOCUMENT NUMBER:          139:110840
TITLE:                    Chymase inhibitors and their therapeutic potential
AUTHOR(S):                Akahoshi, Fumihiko
CORPORATE SOURCE:         Research Laboratory II, Pharmaceuticals Research Unit,
                          Mitsubishi Pharma Corp., Kamoshida-cho, Aoba-ku,
                          Yokohama, 227-0033, Japan
SOURCE:                   Drugs of the Future (2002), 27(8), 765-770
                          CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER:                Prous Science
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
ED   Entered STN:  09 Dec 2002
AB   A review.  Chymase is thought to play important roles in several biol.
     reactions.  With the recent discovery of potent chymase inhibitors
     featuring specificity and metabolic stability, their potential clin.
     application has widened.  Here, chymase inhibitors and their therapeutic
     potential in chymase-induced disease are addressed.  Topics include
     peptidic chymase inhibitors, non-peptidic chymase inhibitors, and
     therapeutic potential of chymase inhibitors in restenosis after bypass
     graft or PTCA, tissue adhesion, angiogenesis-related diseases and atopic
     dermatitis.
IT   130727-22-9
     RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (chymase inhibitors and their therapeutic potential)
RN   130727-22-9  CAPLUS
CN   L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-
     (diphenoxyphosphinyl)-2-phenylethyl]- (9CI)  (CA INDEX NAME)

Absolute stereochemistry.
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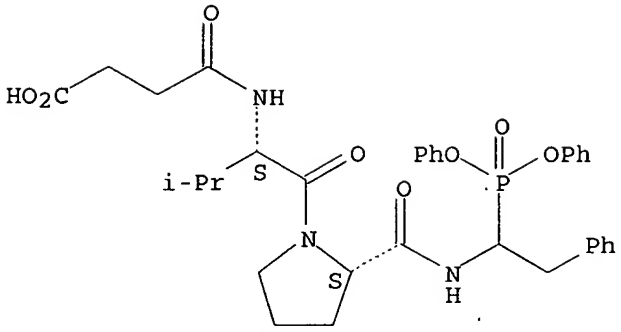
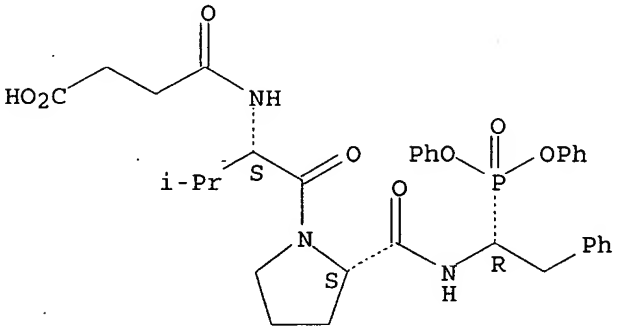


REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L40 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:435917 CAPLUS
DOCUMENT NUMBER: 133:318923
TITLE: Aminophosphonic and aminophosphinic acid derivatives in the design of transition-state analogue inhibitors: biomedical opportunities and limitations
AUTHOR(S): Oleksyszyn, Jozef
CORPORATE SOURCE: Dyax Corporation, Cambridge, MA, USA
SOURCE: Aminophosphonic and Aminophosphinic Acids (2000), 537-557. Editor(s): Kukhar, Valery Pavlovich; Hudson, Harry R. John Wiley & Sons Ltd.: Chichester, UK. CODEN: 69ABMI
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
ED Entered STN: 29 Jun 2000
AB The design of transition-state (TS) analog inhibitors involves the replacement of key enzyme substrate moieties by structurally related mimetics. Aminophosphonic and aminophosphinic acid derivs. are classical examples of such compds., demonstrating that replacement of the carboxylic amino acid moiety provides excellent transition-state analog-type inhibitors for proteolytic enzymes. In addition, phosphonic and phosphinic acid residues can used in the design of hydrolytically stable phosphate mimics of peptides which contain O-phosphorylated tyrosine, serine and threonine. Although it is clear that the utility of aminophosphonic and aminophosphinic acids in drug design is much broader than the simple analogy to amino carboxylic acids would imply, this analogy nonetheless provides the most elegant examples of rational drug design described in the literature. The proteolytic enzymes are primary targets for compds. of this type, and several chapters in the present volume describe in detail the use of phosphonate-type inhibitors for specific enzymes such as HIV aspartyl protease, human collagenase, and thrombin. General principles for the design of TS analog types of inhibitors for proteolytic enzymes are provided in this chapter, along with discussion concerning the importance of some proteolytic enzymes as targets for drug development. Some new data is included which concerns the activity of aminophosphonic-type inhibitors in cell or tissue culture and in the animal model.
IT **174391-82-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(phenylalanine-related phosphonates Cbz-PheP(OPh)2 and Suc-Val-Pro-PheP(OPh)2 inhibit human heart chymase)

RN 174391-82-3 CAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[(1R)-1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L40 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:582644 CAPLUS
DOCUMENT NUMBER: 131:214554
TITLE: Preparation of basic α-aminoalkylphosphonate derivatives as serine protease inhibitors
INVENTOR(S): Powers, James C.; Jackson, Delwin S.; Ni, Liming
PATENT ASSIGNEE(S): Georgia Tech Research Corp., USA
SOURCE: U.S., 18 pp., Cont.-in-part of U.S. 5,686,419.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5952307	A	19990914	US 1997-907840	19970814
US 5686419	A	19971111	US 1994-184286	19940121
PRIORITY APPLN. INFO.:			US 1994-184286 A2	19940121

OTHER SOURCE(S): MARPAT 131:214554
ED Entered STN: 16 Sep 1999
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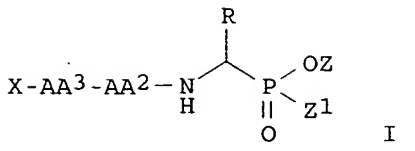

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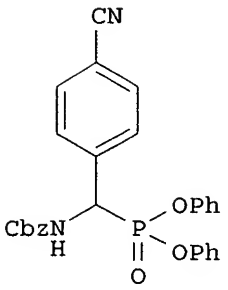

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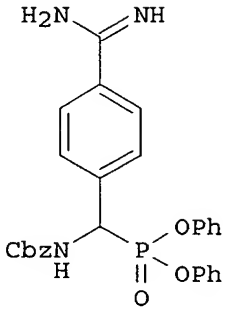


III

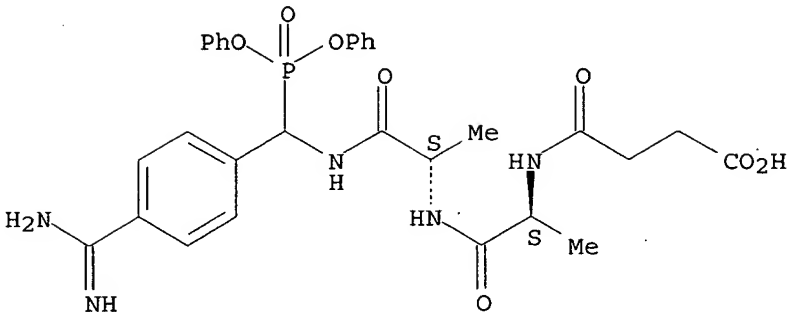
AB Peptidyl α-aminoalkylphosphonic acid diesters with basic substituents I [R = Ph, CH2Ph, C1-6 alkyl substituted with amidino, guanidino, isothioureido, or amino; Z = C1-6 perfluoroalkyl, Ph, Ph substituted with J; Z1 = C1-6 perfluoroalkyloxy, phenoxy, phenoxy substituted with J, C1-6 alkoxy, halo; J = halo, C1-6 alkyl, C1-6 perfluoroalkyl, C1-6 alkoxy, NO2, CN, OH, CO2H, amino, C1-6 alkylamino, C2-12 dialkylamino, C1-6 acyl, C1-6 alkoxycarbonyl, C1-6 alkylthio; AA2, AA3 = independently bond, blocked or unblocked D-, L-, or achiral amino acid residue; X = Y-CO, Y-SO2; Y = Ph-CH:CH, (2-furyl)CH:CH, (2-thienyl)CH:CH, (2-Pyridyl)CH:CH, 2-phenoxyphenyl, 3-phenoxyphenyl, substituted Ph, C1-6 alkenyl substituted with a heterocyclic group, (un)substituted Ph, or (un)substituted naphthyl] and pharmaceutically acceptable salts thereof were prepared as compds. for use in inhibiting serine proteases with trypsin-like specificity and as anti-inflammatory agents, anticoagulants, and anti-tumor agents. Thus, condensation of 9.75 g 4-cyanobenzaldehyde with 7.65 g benzyl carbamate and 13.5 mL tri-Ph phosphite in 20 mL glacial acetic acid gave 70% cyanophenylphosphonate II. Amidation of II with ammonia and ammonium chloride in MeOH gave amidinophenyl derivative III as its HCl salt. III and related compds. were tested for inhibition of a variety of serine proteases.

IT **242817-04-5P 242817-35-2P 242817-39-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of basic α-aminoalkylphosphonate derivs. as serine protease inhibitors)

RN 242817-04-5 CAPLUS

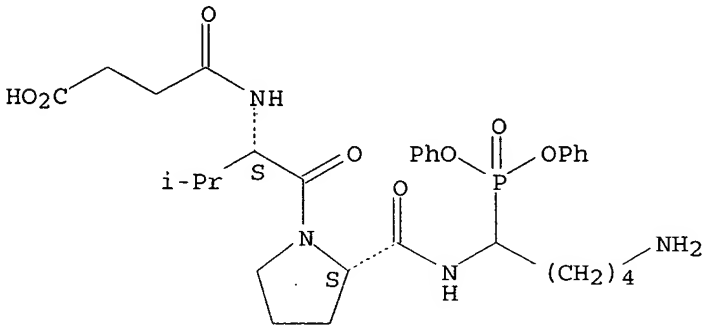
CN L-Alaninamide, N-(3-carboxy-1-oxopropyl)-L-alanyl-N-[[4-(aminoiminomethyl)phenyl](diphenoxyphosphinyl)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



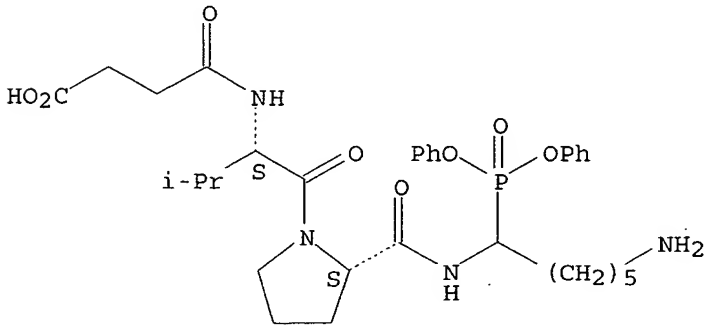
RN 242817-35-2 CAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[5-amino-1-(diphenoxyphosphinyl)pentyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 242817-39-6 CAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[6-amino-1-(diphenoxyphosphinyl)hexyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L40 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:302495 CAPLUS
DOCUMENT NUMBER: 129:80594

TITLE: Purification and characterization of lymphocyte chymase I, a granzyme implicated in perforin-mediated lysis

AUTHOR(S): Woodard, Susan L.; Fraser, Stephanie A.; Winkler, Ulrike; Jackson, Delwin S.; Kam, Chih-Min; Powers, James C.; Hudig, Dorothy

CORPORATE SOURCE: Department of Microbiology, School of Medicine, University of Nevada, Reno, NV, 89557, USA

SOURCE: Journal of Immunology (1998), 160(10), 4988-4993
CODEN: JOIMA3; ISSN: 0022-1767

PUBLISHER: American Association of Immunologists

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 23 May 1998

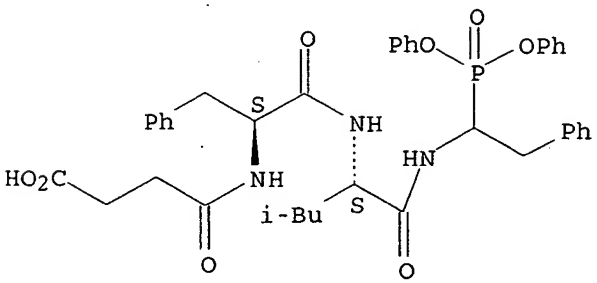
AB One mechanism of killing by cytotoxic lymphocytes involves the exocytosis of specialized granules. The released granules contain perforin, which assembles into pores in the membranes of cells targeted for death. Serine proteases termed granzymes are present in the cytotoxic granules and include several chymases (with chymotrypsin-like specificity of cleavage). One chymase is selectively reactive with an inhibitor, biotinyl-Aca-Aca-Phe-Leu-PheP(OPh)2, that blocks perforin lysis. The authors report the purification and characterization of this chymase, lymphocyte chymase I, from rat natural killer cell (RNK)-16 granules. Lymphocyte chymase I is 30 kDa with a pH 7.5 to 9 optimum and primary substrate preference for tryptophan, a preference distinct from rat mast cell chymases. This chymase also reacts with other selective serine protease inhibitors that block perforin pore formation. It elutes by Cu2+-immobilized metal affinity chromatog. with other granzymes and has the N-terminal protein sequence conserved among granzymes. Chymase I reduces pore formation when preincubated with perforin at 37°. In contrast, addition of the chymase without preincubation had little effect on lysis. It should be noted that the perforin preparation contained sufficient residual chymase activity to support lysis. Thus, the reduction of lysis may represent an effect of excess prolytic chymase I or a means to limit perforin lysis of bystander cells. In contrast, other chymases and granzyme K were without effect when added to perforin during similar preincubation. Identification of the natural substrate of chymase I will help resolve how it regulates perforin-mediated pore formation.

IT **209335-74-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of lymphocyte chymase I by)

RN 209335-74-0 CAPLUS

CN L-Leucinamide, N-(3-carboxy-1-oxopropyl)-L-phenylalanyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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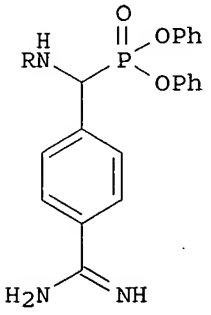
L40 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:338712 CAPLUS
DOCUMENT NUMBER: 129:95705
TITLE: Synthesis and Evaluation of Diphenyl Phosphonate Esters as Inhibitors of the Trypsin-like Granzymes A and K and Mast Cell Tryptase
AUTHOR(S): Jackson, Delwin S.; Fraser, Stephanie A.; Ni, Li-Ming; Kam, Chih-Min; Winkler, Ulrike; Johnson, David A.; Froelich, Christopher J.; Hudig, Dorothy; Powers, James C.
CORPORATE SOURCE: School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA, 30332-0400, USA
SOURCE: Journal of Medicinal Chemistry (1998), 41(13), 2289-2301
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 06 Jun 1998
GI



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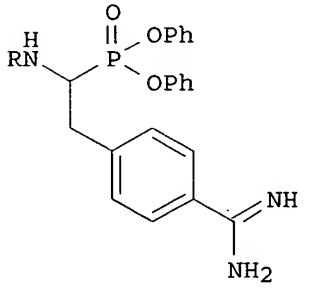


II

AB Thirty-six new amino acid and peptidyl phosphonate esters, e.g. I [R = PhCH2O2C (Cbz), HO2CCH2CH2CO (Suc), R1CH:CHCO, 3-PhOC6H4CO, 2-PhOC6H4CO, 1-C10H7SO2, 1-C10H7CH2O2C, Cbz-X, R2-Pro, Suc-Ala-Ala, Boc-D-Phe-Pro, PhCH2SO2-Gly-Pro; R1 = Ph, 2-furyl, 2-thienyl, 3-pyridyl; X = Ala, Val, Leu, Pro, Thr, Lys, Phe, Ala-Ala, Pro-Ala, Asp-Ala, Asp(OCMe3)-Ala, Lys-Ala, Lys(Boc)-Ala, Phe-Ala, Ala-Ala-Ala; R2 = 2-PhOC6H4CO, 3-PhOC6H4CO, Ph2CHCH2CO, PhCH2CH2CO; Boc = Me3CO2C] were synthesized and evaluated to identify potent and selective inhibitors for four trypsin-like proteases: lymphocyte granzymes A and K, human mast cell tryptase, and pancreatic trypsin. Among five Lys and Arg homologs, II (R = Cbz) is the most potent inhibitor for granzyme A, and CbzNHCH(PO3Ph2)(CH2)4NH2.HCl (III) is the best inhibitor for granzyme K, mast tryptase, and trypsin. Generally, phosphonates I inhibit granzyme A and trypsin more potently than granzyme K and tryptase. Dipeptide phosphonates I (R = Cbz-Ala, Cbz-Thr) are the most potent inhibitors for granzyme A, and I (R = Cbz-Thr) (kobs/[I] = 2220 M-1 s-1) was quite specific with much lower inhibition rates for granzyme K and trypsin (kobs/[I] = 3 and 97 M-1 s-1, resp.) and no inhibition with tryptase. The most effective inhibitor of granzyme A was I (R = PhCH2SO2-Gly-Pro) with a second-order rate constant of 3650 M-1 s-1. The most potent inhibitor for granzyme K was I (R = Ph2CHCH2CO-Pro) with a kobs/[I] = 1830 M-1 s-1; all

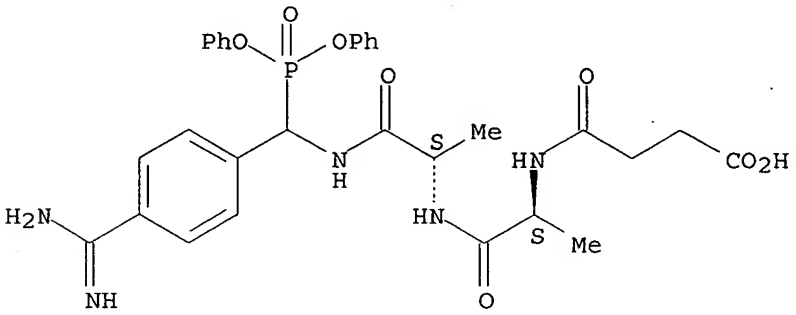
other phosphonates inhibited granzyme K weakly (kobs/[I] < 60 M-1 s-1). Human mast cell tryptase was inhibited slowly by these phosphonates with III as the best inhibitor (kobs/[I] = 89 M-1 s-1). The overall results suggest that scaffolds of II (R = Phe-Thr) and Phe-Pro-Lys will be useful to create selective phosphonate inhibitors for granzymes A and K, resp., and that P4 substituents offer opportunities to further enhance selectivity and reactivity.

IT **209676-15-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and structure-activity of phosphonate ester inhibitors of the trypsin-like granzymes A and K and mast cell tryptase)

RN 209676-15-3 CAPLUS

CN L-Alaninamide, N-(3-carboxy-1-oxopropyl)-L-alanyl-N-[[4-(aminoiminomethyl)phenyl](diphenoxyphosphinyl)methyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

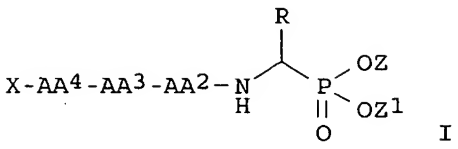
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L40 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:735918 CAPLUS
DOCUMENT NUMBER: 128:3887
TITLE: Preparation of basic α-aminoalkylphosphonate derivatives as serine protease inhibitors
INVENTOR(S): Powers, James C.; Boduszek, Bogdan; Oleksyszyn, Jozef
PATENT ASSIGNEE(S): Georgia Tech Research Corp., USA
SOURCE: U.S., 16 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

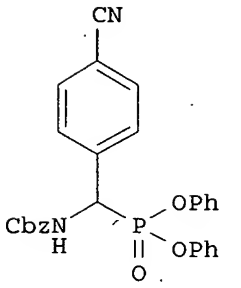
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5686419	A	19971111	US 1994-184286	19940121
US 5952307	A	19990914	US 1997-907840	19970814
PRIORITY APPLN. INFO.:			US 1994-184286 A2	19940121

OTHER SOURCE(S): MARPAT 128:3887

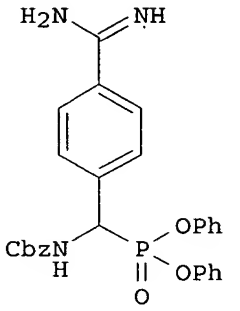
ED Entered STN: 22 Nov 1997
GI



I



II



III

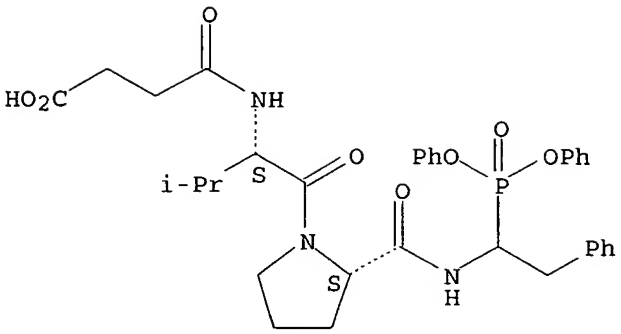
AB Peptidyl α-aminoalkylphosphonic acid diesters with basic substituents I [R = Ph, CH2Ph, C1-6 alkyl substituted with amidino, guanidino, isothioureido, or amino; Z, Z1 = independently C1-6 perfluoroalkyl, Ph, Ph substituted with 0-3 halo, C1-6 alkyl, C1-6 perfluoroalkyl, C1-6 alkoxy, NO2, CN, OH, CO2H, amino, C1-6 alkylamino, C2-12 dialkylamino, C1-6 acyl, C1-6 alkoxycarbonyl, C1-6 alkylthio; AA2, AA3, AA4 = independently bond, blocked or unblocked D-, L-, or achiral amino acid residue; X = H, NH2CO, NH2CS, NH2SO2, YNHCO, YNHCS, YNHSO2, YCS, YSO2, YO2C, YCO; Y = (un)substituted C1-6 alkyl, C1-6 fluoroalkyl, Ph, naphthyl, C1-6 alkylphenyl] and pharmaceutically acceptable salts thereof are prepared as compds. for use in inhibiting serine proteases with trypsin-like specificity and as anti-inflammatory agents, anticoagulants, and anti-tumor agents. Thus, condensation of 9.75 g 4-cyanobenzaldehyde with 7.65 g benzyl carbamate and 13.5 mL tri-Ph phosphite in 20 mL glacial acetic acid gave 70% cyanophenylphosphonate II. Amidination of II with ammonia and ammonium chloride in MeOH gave amidinophenyl derivative III as its HCl salt. III and related compds. were tested for inhibition of a variety of serine proteases.

IT **130727-22-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of basic α-aminoalkylphosphonate derivs. as serine protease inhibitors)

RN 130727-22-9 CAPLUS

CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

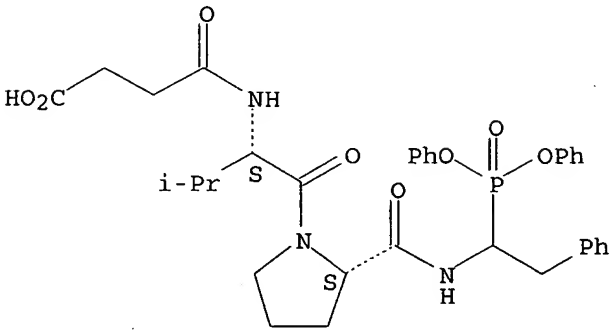
Absolute stereochemistry.



L40 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:687567 CAPLUS
DOCUMENT NUMBER: 126:3707
TITLE: The 1.8 Å crystal structure of human cathepsin G in complex with Suc-Val-Pro-PheP-(OPh)2: a Janus-faced proteinase with two opposite specificities
AUTHOR(S): Hof, Peter; Mayr, Irmgard; Huber, Robert; Korzus, Edward; Potempa, Jan; Travis, James; Powers, James C.; Bode, Wolfram
CORPORATE SOURCE: Max-Planck-Inst. Biochem., Planegg-Martinsried, D-82152, Germany
SOURCE: EMBO Journal (1996), 15(20), 5481-5491
CODEN: EMJODG; ISSN: 0261-4189
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 22 Nov 1996
AB The crystal structure of human neutrophil cathepsin G, complexed with the peptidyl phosphonate inhibitor Suc-Val-Pro-PheP-(OPh)2, has been determined to a resolution of 1.8 Å using Patterson search techniques. The cathepsin G structure shows the polypeptide fold characteristic of trypsin-like serine proteinases and is especially similar to rat mast cell proteinase II. Unique to cathepsin G, however, is the presence of Glu226 (chymotrypsinogen numbering), which is situated at the bottom of the S1 specificity pocket, dividing it into two compartments. For this reason, the benzyl side chain of the inhibitor PheP residue does not fully occupy the pocket but is, instead, located at its entrance. Its pos. charged equatorial edge is involved in a favorable electrostatic interaction with the neg. charged carboxylate group of Glu226. Arrangement of this Glu226 carboxylate would also allow accommodation of a Lys side chain in this S1 pocket, in agreement with the recently observed cathepsin G preference for Lys and Phe at P1. The cathepsin G complex with the covalently bound phosphonate inhibitor mimics a tetrahedral substrate intermediate. A comparison of the Arg surface distributions of cathepsin G, leukocyte elastase and rat mast cell protease II shows no simple common recognition pattern for a mannose-6-phosphate receptor-independent targeting mechanism for sorting of these granular proteinases.
IT **130727-22-9D**, complexes with cathepsin G
RL: PRP (Properties)
(crystal structure of human neutrophil cathepsin G in complex with Suc-Val-Pro-PheP-(OPh)2)
RN 130727-22-9 CAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-

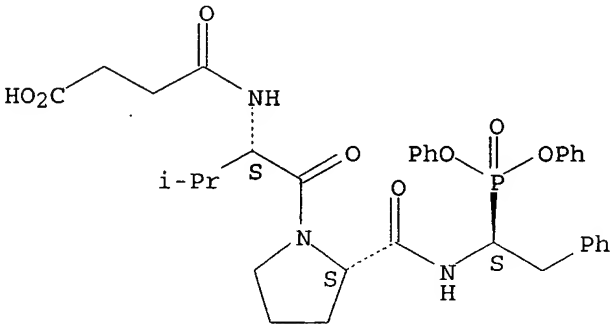
(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **174391-80-1**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibitor binding; crystal structure of human neutrophil cathepsin G in complex with Suc-Val-Pro-PheP-(OPh)2)
RN 174391-80-1 CAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[(1S)-1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

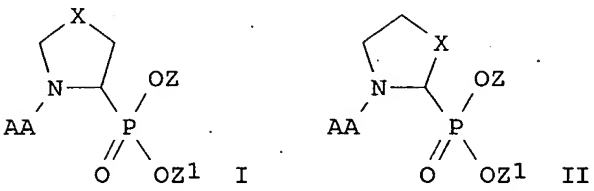
Absolute stereochemistry.



L40 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:153397 CAPLUS
DOCUMENT NUMBER: 124:203102
TITLE: Preparation of peptide containing proline phosphonate derivatives as inhibitors of serine proteases
INVENTOR(S): Powers, James C.; Boduszek, Bogdan; Oleksyszyn, Jozef
PATENT ASSIGNEE(S): Georgia Tech. Research Corp., USA
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9529691 A1 19951109 WO 1995-US5345 19950428
W: CA, JP, MX
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
US 5543396 A 19960806 US 1994-234181 19940428
PRIORITY APPLN. INFO.: US 1994-234181 A 19940428
OTHER SOURCE(S): MARPAT 124:203102
ED Entered STN: 16 Mar 1996
GI



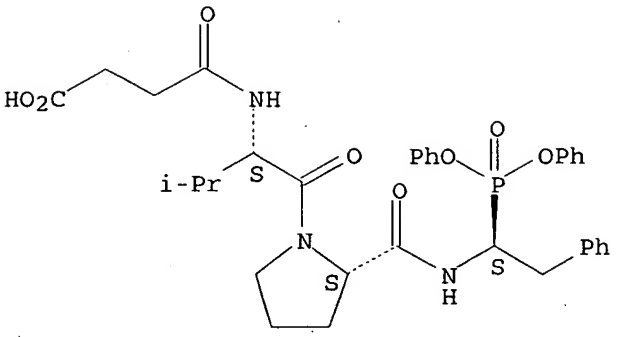
I II

AB Peptidyl derivs. of diesters of α-aminoalkylphosphonic acids, particularly those with proline or related structures, [I and II; Z, Z1 = C1-6 perfluoroalkyl, (un)substituted Ph; X = a single bond, CH2, CH2CH2, (CH2)3, (CH2)4, Y, CH2Y, YCH2, (H,H); Y = O, S; AA = H, PhCH2O2C, H2NCHRCO (wherein R = C1-6 alkyl optionally fluorinated), β-alanine, glycine, ε-aminocaproic acid, sarcosine, side chain (un)blocked L-, D-, or DL-α-amino acid selected from the group consisting of alanine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, and etc.], useful for inhibiting serine proteases with chymotrypsin-like, trypsin-like, elastase-like, and dipeptidyl peptidase IV specificity and their roles as anti-inflammatory agents, anticoagulants, anti-tumor agents, and anti-AIDS agents, are prepared Thus, to 0.36 g Boc-D-Phe-Pro-OH in 2 mL dry DMF at 0°, 0.17 g N,N'-dicyclohexylcarbodiimide was added. After stirring the mixture for 1 h, 0.45 g di-Ph amino(4-amidinophenyl)methanephosphonate dihydrochloride was added the solution was stirred for 48 h to give di-Ph N-(N-tert-butoxycarbonyl-D-phenylalanyl-L-prolyl)amino(4-amidinophenyl)methanephosphonate hydrochloride. H-Ala-ProP(OC6H4Cl-4)2.HCl and H-Ala-PipP(OC6H4Cl-4)2.HCl in vitro at 0.12 mM inhibited human placenta dipeptidylpeptidase IV (DPP-IV) at 0 and 88% after 2 min, resp., and 88 and 100%, resp., after 30 min.

IT **174391-80-1P 174391-82-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptide containing proline phosphonate derivs. as inhibitors of
serine proteases for therapeutics)

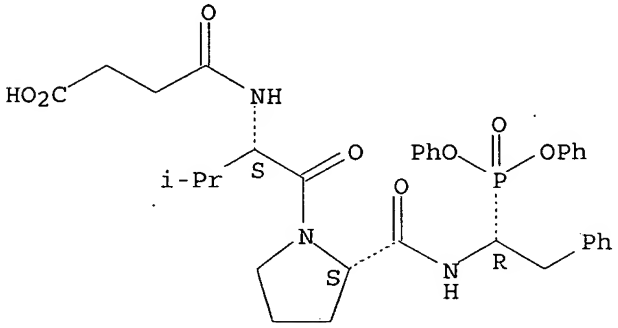
RN 174391-80-1 CAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[(1S)-1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 174391-82-3 CAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[(1R)-1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L40 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:38271 CAPLUS
DOCUMENT NUMBER: 114:38271
TITLE: Irreversible inhibition of serine proteases by peptide derivatives of (α-aminoalkyl)phosphonate diphenyl esters
AUTHOR(S): Oleksyszyn, Jozef; Powers, James C.
CORPORATE SOURCE: Sch. Chem., Georgia Inst. Technol., Atlanta, GA, 30332, USA
SOURCE: Biochemistry (1991), 30(2), 485-93
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 114:38271
ED Entered STN: 09 Feb 1991
AB Peptidyl derivs. of di-Ph (α-aminoalkyl)phosphonates have been synthesized and are effective and specific inhibitors of serine proteases at low concentration Z-PheP(OPh)2 (whereP(OPh)2 refers to the di-Ph phosphonate moiety) irreversibly reacts with chymotrypsin (kobsd/[I] = 1200 M-1 s-1) and does not react with 2 elastases. The best inhibitor for most chymotrypsin-like enzymes including bovine chymotrypsin, cathepsin G, and rat mast cell protease II is the tripeptide Suc-Val-Pro-PheP(OPh)2 which corresponds to the sequence of an excellent p-nitroanilide substrate for

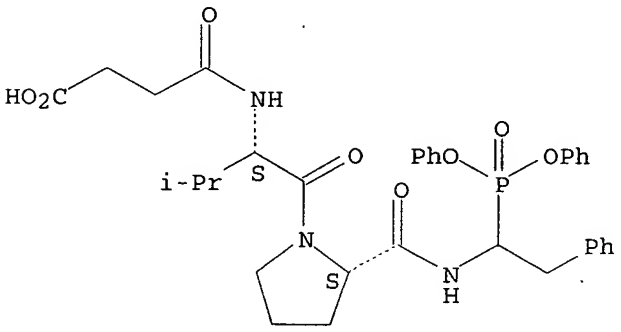
several chymases. The valine derivative Z-ValP(OPh)2 is specific for elastases and reacts with human leukocyte elastase (HLE, 280 M-1 s-1) but not with chymotrypsin. The tripeptide Boc-Val-Pro-ValP(OPh)2, which has a sequence found in a good trifluoromethyl ketone inhibitor of HLE, is the best inhibitor for HLE (kobsd/[I] = 27,000 M-1 s-1) and porcine pancreatic elastase (PPE, kobsd/[I] = 11,000 M-1 s-1). The rates of inactivation of chymotrypsin [by MeO-Suc-Ala-Ala-Pro-PheP(OPh)2] and PPE and HLE [by MeO-Suc-Ala-Ala-Pro-ValP(OPh)2] were decreased 2-5-fold in the presence of the corresponding substrate, which demonstrates active site involvement. Only one of two diastereomers of Suc-Val-Pro-PheP(OPh)2 reacts with chymotrypsin (146,000 M-1 s-1), and the enzyme-inhibitor complex had one broad signal at 25.98 ppm in the 31P NMR spectrum corresponding to the Ser-195 phosphonate ester. Phosphonylated serine proteases are extremely stable since the half-time for reactivation was >48 h for the inhibited elastases and 7.5-26 h for chymotrypsin. Peptidyl derivs. of di-Ph (α-aminoalkyl)phosphonates are relatively easy to synthesize, are chemical stable in buffer and in human plasma, form very stable derivs. with serine proteases, do not react with acetylcholinesterase, and thus should have considerable potential utility as therapeutic agents.

IT **130727-22-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and serine proteinases inactivation by, inhibitor structure and stereochem. in relation to)

RN 130727-22-9 CAPLUS

CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L40 ANSWER 10 OF 12 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-213039 [20] WPIX
DOC. NO. CPI: C2004-084451
TITLE: Prevention or reduction of adhesion formation between tissue surfaces in vertebrate subject by administering to the subject protease inhibitors to site on tissue surface.
DERWENT CLASS: A96 B04
INVENTOR(S): MIYAZAKI, M
PATENT ASSIGNEE(S): (MIYA-I) MIYAZAKI M
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2004018984	A1	20040129	(200420)*		17

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2004018984	A1 Provisional	US 2002-396493P	20020717
		US 2003-602035	20030623

PRIORITY APPLN. INFO: US 2002-396493P 20020717; US 2003-602035 20030623

ED 20040324

AN 2004-213039 [20] WPIX

AB US2004018984 A UPAB: 20040324

NOVELTY - Adhesion formation between tissue surfaces in a vertebrate subject is prevented or reduced by administering to the subject at least one protease inhibitor to a site on a tissue surface.

ACTIVITY - Vulnerary.

MECHANISM OF ACTION - Serine protease inhibitor.

Mature female Syrian hamsters were anesthetized with intraperitoneal sodium pentobarbital (50 mg/kg). An abdominal midline incision was made, and the right uterus was grasped and denuded of serosa over half the length of the uterine body until punctate hemorrhage occurred, using a swab. In the chymase-treated group, 1 m of 10 micro m Suc-Val-Pro-Phe-P(OPh)2 in saline was injected into the abdomen. The abdomen was closed in two layers with silk sutures. Three days after the surgery, the animals were anesthetized with sodium pentobarbital (50 mgikg, i.p.) and the uterus was removed for the measurement of chymase activity. Two weeks after surgery, the animals were anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and the adhesions were assessed.

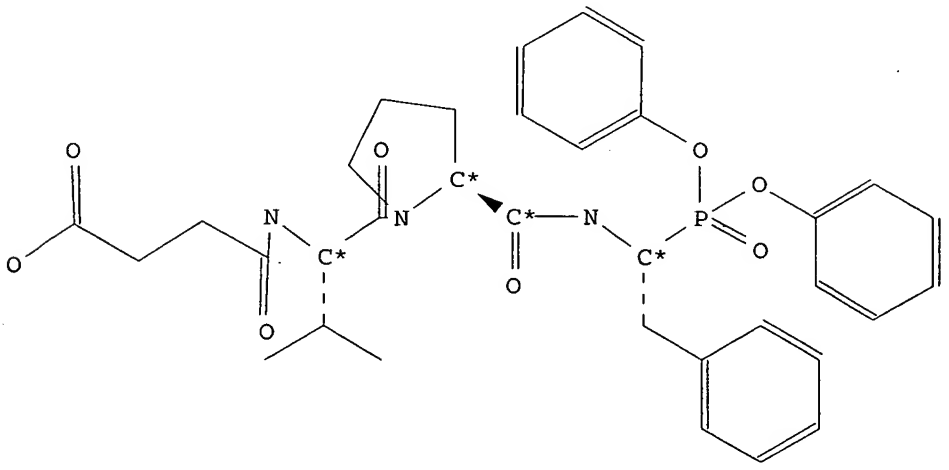
USE - For preventing or reducing adhesion formation between tissue surfaces in vertebrate subject, i.e. human.

ADVANTAGE - The invention prevents or reduces the adhesion promotion that is a common consequence following surgical procedures, including, e.g. cardiac, thoracic, gynecologic, ophthalmic, and abdominal surgeries.

Dwg.0/6

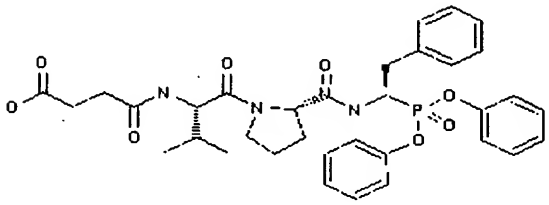
DCSE 399806-1-0-0

SDCN RADD0D



L40 ANSWER 11 OF 12 PROUSDDR COPYRIGHT 2006 PROUS SCIENCE on STN
ACCESSION NUMBER: 2000:7960 PROUSDDR
DOCUMENT NUMBER: 292592
CHEMICAL NAME: N-(3-Carboxypropanoyl)-L-valyl-N-(1(S)-(diphenoxyphosphinyl)-2-phenylethyl)-L-prolinamide
CAS REGISTRY NUMBER: **174391-80-1**
MOLECULAR FORMULA: C34 H40 N3 O8 P
HIGHEST DEV. PHASE: PRECLINICAL
ORIGINATOR: Dyax
Osaka Medical College
CLASSIFICATION CODE: Restenosis Treatment of; Atherosclerosis Therapy
OTHER SOURCE: SYNTHLINE 2001000639
ENTRY DATE: Entered STN: 9 May 2004
Last Updated on STN: 3 Jan 2006

STRUCTURE:



PROUS REFERENCES:
RefID: 592164 (Text Available)
Drug Data Report, Vol. 22, No. 11, pp 995, 2000

REFERENCE TEXT: RefID: 592164
ACTION - Chymase inhibitor able to prevent vascular proliferation in dogs undergoing right carotid artery bypass grafting with the ipsilateral external jugular vein; compound infiltrated into the grafted vein at a concentration of 10 mcM reduced the intimal area of grafted vein by 63.9% compared to controls. Potentially useful for the prevention of vascular diseases such as vascular proliferation in grafted vessels.

PATENT REFERENCES:

TITLE: Proline phosphonate derivatives
INVENTOR(S): Powers, J.C.; Oleksyszyn, J.; Boduszek, B.
PATENT ASSIGNEE(S): Georgia Technology
PATENT INFORMATION: WO 9529691 19951109
PRIORITY INFORMATION: US 1994-234181 19940428

TITLE: Basic alpha-aminoalkylphosphonate derivatives
INVENTOR(S): Powers, J.C.; Jackson, D.S.; Ni, L.
PATENT ASSIGNEE(S): Georgia Technology
PATENT INFORMATION: US 5952307 19990914
PRIORITY INFORMATION: US 1997-907840 19970814

REFERENCES:

(1) RefID: 594948, Periodic Publication
"Irreversible inhibition of serine proteases by peptide derivatives of (alpha-aminoalkyl)phosphonate diphenyl esters"
Oleksyszym, J.; Powers, J.C., Biochemistry, Vol. 30, No. 2, pp 485, 1991

(2) RefID: 594947, Periodic Publication
"The 1.8 Å crystal structure of human cathepsin G in complex with Suc-Val-Pro-PheP-(OPh)2: A Janus-faced proteinase with two opposite specificities"
Hof, P.; et al., EMBO J, Vol. 15, No. 20, pp 5481, 1996

(3) RefID: 588751, Periodic Publication
"Chymase inhibitor prevents vascular proliferation in dog grafted veins"
Takai, S.; Yuda, A.; Jin, D.; Sakaguchi, M.; Nishimoto, M.; Sasaki, S.; Miyazaki, M., J Hypertens, Vol. 18, No. Suppl. 4, (Abst P4.45), 2000

(4) RefID: 594946, Periodic Publication
"Inhibition of chymase reduces vascular proliferation in dog grafted veins"
Takai, S.; et al., FEBS Lett, Vol. 467, No. 2-3, pp 141, 2000

(5) RefID: 657719, Periodic Publication
"Chymase inhibitor suppresses adhesion formation in a hamster experimental model"
Okamoto, Y.; et al., Eur J Pharmacol, Vol. 435, No. 2-3, pp 265, 2002

(6) RefID: 667135, Congress Literature
"Effect of chymase inhibitor on postoperative wound healing after trabeculectomy in canine eyes"
Maruichi, M.; et al., Annu Meet Assoc Res Vision Ophthalmol (ARVO), May 5 2002-May 10 2002, Fort Lauderdale, (Abst 3347)

(7) RefID: 675442, Periodic Publication
"Chymase inhibitors may prevent postoperative adhesion formation"
Okamoto, Y.; Takai, S.; Yamada, M.; Miyazaki, M., Fertil Steril, Vol. 77, No. 5, pp 1044, 2002

(8) RefID: 744672, Periodic Publication
"Role of chymase in vascular diseases and the efficacy of chymase inhibitor"
Takai, S., Folia Pharmacol Jpn, Vol. 122, No. 2, pp 111, 2003

(9) RefID: 744695, Periodic Publication
"Lengthy suppression of vascular proliferation by a chymase inhibitor in dog grafted veins"
Tsunemi, K.; Takai, S.; Nishimoto, M.; et al., J Thorac Cardiovasc Surg, Vol. 124, No. 3, pp 621, 2003

(10) RefID: 942880, Periodic Publication
"Effect of chymase on intraocular pressure in rabbits"
Konno, T.; et al., Eur J Pharmacol, Vol. 524, No. 1-3, pp 132, 2005

START LOCAL KERMIT RECEIVE PROCESS

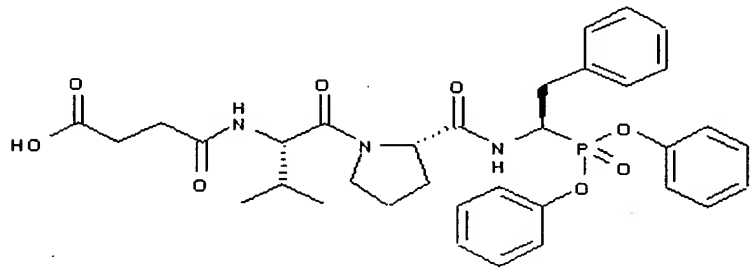
BINARY DATA HAS BEEN DOWNLOADED TO MULTIPLE FILES 'IMAGEnnn.TIF'

L40 ANSWER 12 OF 12 SYNTHLINE COPYRIGHT 2006 PROUS SCIENCE on STN

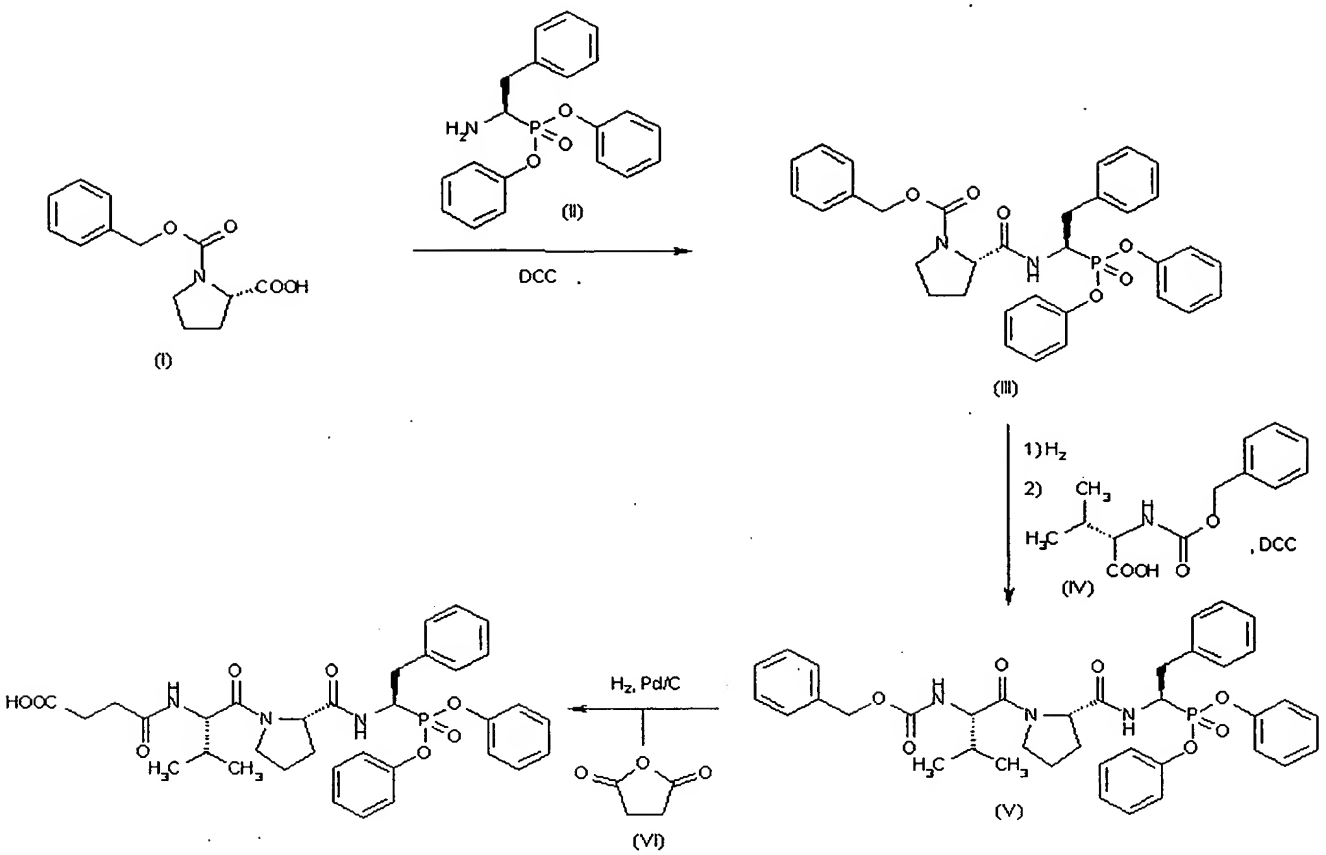
Searched by Barb O'Bryen, STIC 2-2518

ACCESSION NUMBER: 2001:639 SYNTHLINE
ENTRY NUMBER: 292592
CHEMICAL NAME: N-(3-Carboxypropanoyl)-L-valyl-N-(1(S)-(diphenoxyphosphinyl)-2-phenylethyl)-L-prolinamide
CAS REGISTRY NO.: **174391-80-1**
MOLECULAR FORMULA: C34 H40 N3 O8 P
MOLECULAR WEIGHT: 649.68
CLASSIFICATION CODE: Atherosclerosis Therapy; Cardiovascular Drugs; Restenosis Treatment of; Treatment of Disorders of the Coronary Arteries and Atherosclerosis; Chymase Inhibitors
HIGHEST DEV. PHASE: Preclinical
COMPANY: Dyax; Osaka Medical College
ENTRY DATE: Entered STN: 16 May 2001
Last Updated on STN: 15 Sep 2006

STRUCTURE:



REACTION: 29259201a
TEXT:
Coupling of PhCH2OOC-Pro-OH (I) with diphenyl (1-amino-2-phenylethyl)phosphonate (II) by means of DCC in THF affords derivative (III), which is then subjected to hydrogenation followed by coupling with PhCH2OOC -Val-OH (IV) by means of DCC to provide peptide derivative (V). Finally, reaction of (V) with succinic anhydride in EtOAc under an atmosphere of H2 in the presence of Pd/C provides the target compound.



TITLE: Irreversible inhibition of serine proteases by peptide derivatives of (alpha-aminoalkyl)phosphonate diphenyl esters
AUTHOR(S): Oleksyszym, J.; Powers, J.C.
SOURCE: Biochemistry (1991), 30(2), 485

TITLE: Basic alpha-aminoalkylphosphonate derivs.
INVENTOR(S): Jackson, D.S.; Ni, L.; Powers, J.C.
PATENT ASSIGNEE(S): Georgia Technology Research Corp.
PATENT INFORMATION: US 5952307

REACTANT IDENTIFIER: (VI) 11291
CHEMICAL NAME: Dihydro-2,5-furandione; Succinic anhydride
CAS REGISTRY NO.: 108-30-5
MOLECULAR FORMULA: C4 H4 O3
MOLECULAR WEIGHT: 100.07
COMPANY: ABCR GmbH & Co.; Acros Organics; Aldrich; Alfa Aesar; American Radiolabeled Chemicals, Inc.; Chem-Impex International, Inc.; Chizhou Sanyuan Chemistry Co., Ltd.; DSM Fine Chemicals Inc.; Fluka; Gallade Chemical Inc.; Graham Chemical Corporation; Harcros Chemicals Inc.; Independent Chemical Corporation; John R. Hess & Company, Inc.; Lancaster Synthesis Inc.; MP Biomedicals; Parchem Trading Ltd.; Pfaltz & Bauer, Inc.; Sigma Chemical Company; Spectrum Quality Products, Inc.; Taizhou Yanling Refined Chemical Co., Ltd.; TCI; Thirumalai Chemicals Ltd.; Tianjin Chemical Reagent No. 1 Plant; U. S. Chemicals, Inc.; Ultimate Chem (India)

Searched by Barb O'Bryen, STIC 2-2518

Pvt. Ltd.; Westco Chemicals Inc.

REACTANT IDENTIFIER: (IV) 18092
CHEMICAL NAME: (2S)-2-(((benzyloxy)carbonyl)amino)-3-methylbutyric acid
MOLECULAR FORMULA: C13 H17 N O4
MOLECULAR WEIGHT: 251.28
COMPANY: Acros Organics; Advanced ChemTech; Aldrich; Alfa Aesar; Chem-Impex International, Inc.; Fluka; Indofine Chemical Company, Inc.; Isochem, Groupe SNPE; KingChem Inc.; Lancaster Synthesis Inc.; MP Biomedicals; Norchim S.A.; Pfaltz & Bauer, Inc.; PPG-Sipsy; Research Organics; Sigma Aldrich Library of Rare Chemicals; Sigma Chemical Company; Synthetech Inc.; TCI

REACTANT IDENTIFIER: (I) 19113
CHEMICAL NAME: (2S)-1-((benzyloxy)carbonyl)-2-pyrrolidinecarboxylic acid
CAS REGISTRY NO.: 1148-11-4
MOLECULAR FORMULA: C13 H15 N O4
MOLECULAR WEIGHT: 249.27
COMPANY: ABCR GmbH & Co.; Acros Organics; Advanced ChemTech; Aldrich; Chem-Impex International, Inc.; Fluka; Indofine Chemical Company, Inc.; Isochem, Groupe SNPE; Lancaster Synthesis Inc.; MP Biomedicals; Pfaltz & Bauer, Inc.; Research Organics; Senn Chemicals AG; Sichuan Sangao Biochemical Co., Ltd.; Sigma Chemical Company; Synthetech Inc.; TCI

REACTANT IDENTIFIER: (II) 44216
CHEMICAL NAME: diphenyl (1R)-1-amino-2-phenylethylphosphonate
MOLECULAR FORMULA: C20 H20 N O3 P
MOLECULAR WEIGHT: 353.36

REACTANT IDENTIFIER: (III) 44217
CHEMICAL NAME: benzyl (2S)-2-((((1R)-1-(diphenoxyphosphoryl)-2-phenylethyl)amino)carbonyl)-1-pyrrolidinecarboxylate
MOLECULAR FORMULA: C33 H33 N2 O6 P
MOLECULAR WEIGHT: 584.61

REACTANT IDENTIFIER: (V) 44218
CHEMICAL NAME: diphenyl (1R)-1-((((2S)-1-((2S)-2-(((benzyloxy)carbonyl)amino)-3-methylbutanoyl)pyrrolidinyl)carbonyl)amino)-2-phenylethylphosphonate
MOLECULAR FORMULA: C38 H42 N3 O7 P
MOLECULAR WEIGHT: 683.75

START LOCAL KERMIT RECEIVE PROCESS

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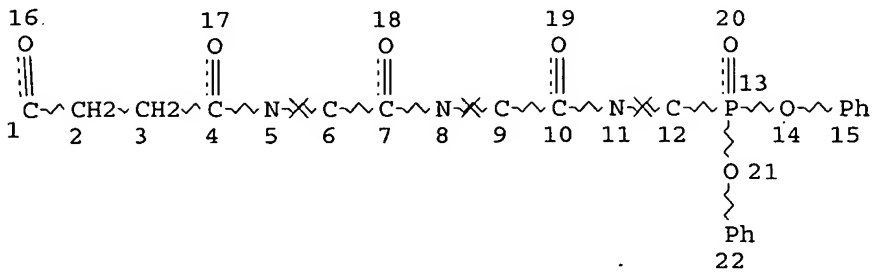
L6 STR



NODE ATTRIBUTES:
NSPEC IS RC AT 5
NSPEC IS RC AT 6
NSPEC IS RC AT 8
NSPEC IS RC AT 9
NSPEC IS RC AT 11
NSPEC IS RC AT 12
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE
L8 8 SEA FILE=REGISTRY SSS FUL L6

100.0% PROCESSED 199 ITERATIONS 8 ANSWERS
SEARCH TIME: 00.00.01

(FILE 'HOME' ENTERED AT 11:05:25 ON 27 SEP 2006)

FILE 'CAPLUS' ENTERED AT 11:05:48 ON 27 SEP 2006
E US2005-544254/APPS
L1 1 SEA ABB=ON US2005-544254/AP
D SCAN
SEL RN

FILE 'REGISTRY' ENTERED AT 11:06:19 ON 27 SEP 2006
L2 6 SEA ABB=ON (130727-22-9/BI OR 174391-80-1/BI OR 37259-58-8/BI
OR 9001-92-7/BI OR 9004-07-3/BI OR 97501-92-3/BI)
D SCAN

FILE 'STNGUIDE' ENTERED AT 11:08:31 ON 27 SEP 2006

FILE 'REGISTRY' ENTERED AT 11:10:16 ON 27 SEP 2006
L3 0 SEA ABB=ON L2 AND PS/FS

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     FILE 'LCA' ENTERED AT 11:17:34 ON 27 SEP 2006
L4             3 SEA ABB=ON  SUC
               D KWIC 1-3

     FILE 'LREGISTRY' ENTERED AT 11:19:13 ON 27 SEP 2006
               E SUCCINYL
L5            31 SEA ABB=ON  SUCCINYL/BI
               D KWIC STR 1-3
               D KWIC STR 10-13

     FILE 'REGISTRY' ENTERED AT 11:21:04 ON 27 SEP 2006
L6             STR
L7             0 SEA SSS SAM L6
L8             8 SEA SSS FUL L6
               SAVE TEMP L8 AUD254FULL/A
               D LC 1-8

     FILE 'CAPLUS' ENTERED AT 11:26:38 ON 27 SEP 2006
L9            19 SEA ABB=ON  L8
L10         2690 SEA ABB=ON  MIYAZAKI M?/AU
L11          577 SEA ABB=ON  TAKAI S?/AU
L12          132 SEA ABB=ON  L10 AND L11
L13       160422 SEA ABB=ON  ADHESION#/OBI
L14           15 SEA ABB=ON  L12 AND L13
               D SCAN L1
L15          372 SEA ABB=ON  (ARYL/OBI OR PHENYL/OBI)(L)DIESTER#/OBI
L16            2 SEA ABB=ON  L12 AND L15
L17            2 SEA ABB=ON  (L10 OR L11) AND L15
               E  ADHESION, BIOLOGICAL+ALL/CT
L18           10 SEA ABB=ON  L14 AND PHARMAC?/SX,SC

     FILE 'STNGUIDE' ENTERED AT 11:29:47 ON 27 SEP 2006

     FILE 'MEDLINE, DRUGU, JICST-EPLUS, BIOSIS, EMBASE, WPIX' ENTERED AT
     11:31:11 ON 27 SEP 2006
L19        10240 SEA ABB=ON  MIYAZAKI M?/AU
L20         2856 SEA ABB=ON  TAKAI S?/AU
L21       567006 SEA ABB=ON  ADHESION#
L22          251 SEA ABB=ON  (ARYL OR PHENYL)(3A)(DIESTER# OR DI ESTER#)
L23            3 SEA ABB=ON  (L19 OR L20) AND L22
L24           58 SEA ABB=ON  L19 AND L20 AND L21
L25           13 SEA ABB=ON  ?PEPTIDE? AND L24

     FILE 'MEDLINE, DRUGU, JICST-EPLUS, BIOSIS, EMBASE, WPIX' ENTERED AT
     11:33:15 ON 27 SEP 2006
               D QUE L23
               D QUE L25
L26           15 SEA ABB=ON  L23 OR L25

     FILE 'CAPLUS' ENTERED AT 11:33:34 ON 27 SEP 2006
               D QUE L1
               D QUE L17
               D QUE L18
L27           11 SEA ABB=ON  (L1 OR L17 OR L18)

     FILE 'CAPLUS, MEDLINE, DRUGU, JICST-EPLUS, EMBASE, WPIX' ENTERED AT
     11:33:44 ON 27 SEP 2006
L28           19 DUP REM L27 L26 (7 DUPLICATES REMOVED)
                    ANSWERS '1-11' FROM FILE CAPLUS
                    ANSWERS '12-13' FROM FILE MEDLINE
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                    ANSWERS '14-17' FROM FILE JICST-EPLUS
                    ANSWER '18' FROM FILE EMBASE
                    ANSWER '19' FROM FILE WPIX

     FILE 'STNGUIDE' ENTERED AT 11:34:24 ON 27 SEP 2006

     FILE 'CAPLUS' ENTERED AT 11:34:41 ON 27 SEP 2006
L29           10 SEA ABB=ON  L9 AND (L10 OR L11)

     FILE 'CAPLUS' ENTERED AT 11:35:39 ON 27 SEP 2006
                D QUE L1
                D QUE L17
                D QUE L18
                D QUE L29
L30           17 SEA ABB=ON  (L1 OR L17 OR L18 OR L29)

     FILE 'CAPLUS, MEDLINE, DRUGU, JICST-EPLUS, EMBASE, WPIX' ENTERED AT
     11:36:07 ON 27 SEP 2006
L31           24 DUP REM L30 L26 (8 DUPLICATES REMOVED)
                    ANSWERS '1-17' FROM FILE CAPLUS
                    ANSWERS '18-19' FROM FILE MEDLINE
                    ANSWERS '20-23' FROM FILE JICST-EPLUS
                    ANSWER '24' FROM FILE EMBASE
                D IBIB ED ABS HITSTR 1-17
                D IBIB ED ABS 18-24

     FILE 'REGISTRY' ENTERED AT 11:36:41 ON 27 SEP 2006
                D STAT QUE L8

     FILE 'WPIX' ENTERED AT 11:36:54 ON 27 SEP 2006
L32             0 SEA SSS SAM L6
L33             1 SEA SSS FUL L6
                D SCAN
L34             1 SEA ABB=ON  L33/DCR
                D SDCN SDRN DCSE
                D SDCN SDRN DCSE L33
L35             1 SEA ABB=ON  RADD0D/DCN OR 399806-1-0-0/DCRE
                D SCAN
                D SCAN L34
L36             1 SEA ABB=ON  L34 OR L35

     FILE 'MARPAT' ENTERED AT 11:50:51 ON 27 SEP 2006

     FILE 'STNGUIDE' ENTERED AT 11:51:17 ON 27 SEP 2006

     FILE 'CAPLUS' ENTERED AT 11:51:49 ON 27 SEP 2006
L37           19 SEA ABB=ON  L8
L38            9 SEA ABB=ON  L37 NOT L30

     FILE 'PROUSDDR, SYNTHLINE' ENTERED AT 11:52:29 ON 27 SEP 2006
L39            2 SEA ABB=ON  L8

     FILE 'WPIX' ENTERED AT 11:52:39 ON 27 SEP 2006
                D STAT QUE L33
                D QUE NOS L36

     FILE 'CAPLUS, WPIX, PROUSDDR, SYNTHLINE' ENTERED AT 11:53:14 ON 27 SEP
     2006
L40           12 DUP REM L38 L36 L39 (0 DUPLICATES REMOVED)
                    ANSWERS '1-9' FROM FILE CAPLUS
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                ANSWER '10' FROM FILE WPIX
                ANSWER '11' FROM FILE PROUSDDR
                ANSWER '12' FROM FILE SYNTHLINE
          D IBIB ED ABS HITSTR 1-10
          D IALL 11-12

FILE 'HOME' ENTERED AT 11:53:43 ON 27 SEP 2006
          D STAT QUE L8

=>
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